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Modifiable Contributors to Cognition in Breast Cancer Survivors

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Modifiable Contributors to Cognition in Breast Cancer Survivors

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Dedication

I dedicate this to my parents, Chris and Pat Henneghan, who have supported me unconditionally and emphasized the value of education for as long as I can remember. Thank you for planting the seeds and continuing to foster the growth of the qualities I needed to get to this point in my life—tenacity, drive, and simply saying “yes” to the opportunities that life presents.

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Modifiable Contributors to Cognition in Breast Cancer Survivors

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Cognitive dysfunction following breast cancer treatment is a serious and pervasive problem. The underlying mechanisms of cancer related cognitive impairments remain unclear, but there is consensus within the scientific community that the causes are multifactorial. This non-experimental, cross-sectional study is an analysis of data from 75 breast cancer survivors six months to 10 years post chemotherapy. The purpose of this study was to identify modifiable psychosocial and behavioral factors that may contribute to cognitive function both directly and indirectly through inflammatory mediators.

Non-linear regression models were used to determine whether stress, perceived social isolation, physical activity, sleep quality, and inflammation are significant predictors of cognitive function. Hierarchical multiple regression was used to determine the unique variance of cognitive function (perceived and performance) explained by the predictor variables. Non-parametric regression was used to illustrate the complex relationships between the psychosocial and behavioral factors and cytokines, and between the cytokines and cognitive outcomes. Mediation analyses were used to gain a better understanding of how the psychosocial variables influence perceived cognitive function.

The findings from this study suggest that perceived stress and loneliness contribute to perceived cognitive functioning in breast cancer survivors but that elevated IL-6 and TNF-α do not mediate these effects. Non-parametric regression graphing illustrated that the cytokines were related to the predictor variables and that cognitive outcomes were related to the cytokines but that the relationships varied in direction and magnitude across levels.

This study provides new knowledge on inflammation and cognitive function six months to 10 years after breast cancer chemotherapy using a biobehavioral model to simultaneously evaluate modifiable psychosocial and behavioral factors that contribute to cognitive function in breast cancer survivors. Findings from this study provide initial evidence for needed future prospective and translational studies to improve cognitive function in breast cancer survivors.

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Chapter 1: Introduction

Improvements in cancer screening, diagnoses, and treatment have resulted in a growing cancer survivorship cohort, especially breast cancer survivors (BCS). Approximately 22% of the estimated 13 million cancer survivors in the United States are BCS (ACS, 2013). Cancer is now considered a chronic condition (Meyers, 2013) that includes long-term mental and physical effects after diagnoses and treatment (IOM, 2009). One of the most distressing (Boykoff, Moieni, & Subramanian, 2009), feared (Ganz et al., 2013) and prevalent (Janelsins, Kesler, Ahles, & Morrow, 2014) long-term effects of treatment that BCS face are problems with cognitive function (deficits in the cognitive domains of memory, attention, processing speed, and executive functioning) (Janelsins et al., 2014; Wefel & Schagen, 2012).

Longitudinal studies utilizing neuropsychological (NP) assessment of cognitive function indicate that up to 30% of cancer patients experience problems with cognitive function prior to treatment; 75% experience problems during primary treatment; and up to 35% experience cognitive problems for months to years after treatment ends (Janelsins et al., 2014). One study found that 30-40% of survivors may experience worsening of cognitive function over time (Wefel, Saleeba, Buzdar, & Meyers, 2010).

BACKGROUND AND SIGNIFICANCE

Problems with cognitive function in survivors can impede daily functioning and quality of life (Duijits et al., 2014) and have a profound negative impact on social functioning, occupational performance, and overall well being (Nelson & Suls, 2013). For example, decreased work productivity and social role performance have been reported in survivors with cognitive problems as opposed to those without them (Reid-Arndt, 2009; Wefel, Lenzi, Theriault, & Buzdar, 2004). Unfortunately, there are limited

treatment options and no clinical guidelines for the amelioration of problems with cognitive function in cancer survivors.

The mechanisms underlying problems with cognitive function in BCS remain unclear, but direct and indirect neurotoxic effects of chemotherapy are the leading candidates (Janelsins et al., 2011; Saykin & Ahles, 2007; Vardy, 2009). Recent research findings indicate that elevated inflammation (estimated by pro-inflammatory markers) may mediate the problems with cognitive function both during and after chemotherapy (Cheng et al., 2014; Ganz et al., 2013; Janelsins et al., 2012; Kesler et al., 2013; Pomykala et al., 2013).

Several individual and treatment related risk factors for problems with cognitive function have been identified in BCS. Those with the most supporting evidence include individual factors— older age (Ahles, Root, & Ryan, 2012; Janelsins et al., 2014; Mandelblatt et al., 2013; Ono et al., 2015; Wefel & Schagen, 2012) and lower cognitive reserve (estimated by educational attainment, IQ; Kesler et al., 2013; Wefel, Witgert, Meyers, 2008). Additionally, breast cancer treatment factors have been identified as risk factors for problems with cognitive functioning such as certain types of chemotherapy. Treatment with anthracycline- based chemotherapy has shown more neural damage than 5-FU chemotherapy in vitro (Tsvetkov, 2016), and worse cognitive performance (verbal learning) in BCS than those treated with non-anthracycline based chemotherapy (Kesler & Blaney, 2016). Some research suggests that treatment with selective estrogen receptor modulators (i.e. tamoxifen) is associated with poorer cognitive function but more research is needed (Janelsins et al., 2012; Jim et al., 2012; Schilder et al., 2009). Importantly, these individual and treatment related factors (age, education, treatment with anthracycline or tamoxifen) are largely not modifiable or unavoidable when faced with a breast cancer diagnosis. Researchers have also consistently found relationships between

emotional distress (i.e. depression and anxiety; Asher, 2011; Poppelreuter et al., 2004; Pullens, De Vries, & Roukema, 2010), fatigue (Bower & Lamkin, 2013; Cheung, Lim, Ho, & Chan, 2013; Hodgson, Hutchinson, Wilson, & Nettelbeck, 2013; Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012), and problems with cognitive function in BCS. Preliminary data also suggests connections between cognitive functioning and hours of sleep (Hartman et al., 2015) and physical activity (Hartman et al., 2015).

Even though evidence supports relationships between the aforementioned individual, treatment-related, emotional factors (depression, anxiety, fatigue) and cancer-related cognitive impairments (CRCI), these factors do not completely explain why a subgroup of BCS who undergo chemotherapy experience persistent problems with cognitive function after treatment ends. Therefore, other factors must be contributing to the manifestation and vulnerability to cognitive impairments and/or decline.

It is possible that factors other than individual demographic and treatment-related factors may contribute to cognitive function either directly or indirectly, through inflammatory mediators. For instance, stress (Aggarwal et al., 2014; Carlson, Speca, Faris, & Patel, 2007), physical activity (Beavers, Brinkley, & Nicklas, 2010; Bherer, 2013), social isolation (Cacioppo & Hawkley, 2009; Yang, McClintock, Kozloski, & Li, 2013), and sleep quality (Clevenger et al., 2012; Miller et al., 2009; Sprod et al., 2010) have been associated with inflammation and cognitive function in similar populations but have not been empirically evaluated in BCS.

CONCEPTUAL FRAMEWORK

For this study, Kang, Rice, Park, Turner-Henson, & Downs' (2010) integrated biobehavioral model provided a framework for exploring the impact of modifiable factors on inflammation and cognitive function in BCS. This model posits six domains, factors

across and within which interact to explain biobehavioral interactions and health outcomes. The six domains include individual, psychosocial, behavioral, environmental, biological, and health and health-related outcomes. Most often, factors across and within the first four domains, individually or in combination, influence biological responses, which, in turn, influence health outcomes. However, under specific context or inquiry, biological factors may also be conceptualized as a moderator along with other factors to influence health outcomes. This model has integrated the strengths of three theoretical models— Stress and Coping Model (Lazarus & Folkman, 1984), Physiological Model of Stress (Selye, 1974), and Allostatic Load Model (McEwen, 1998, 2003), all of which have been extensively studied but individually have weaknesses when applied to biobehavioral research. The model iteration proposed by Kang et al. (2010) offers conceptual and propositional flexibility, and has been adapted for this dissertation study into the framework depicted in Figure 1.1.

The conceptual model for this study includes individual factors (age, cognitive reserve [estimated by education], BMI, history of anthracycline-based chemotherapy, tamoxifen use,) as potential covariates, which have been selected for their relevance to inflammation and cognitive function. The study model incorporates modifiable psychosocial factors (stress, social isolation, emotional distress), and modifiable behavioral factors (physical activity, sleep quality, fatigue) that are known to influence both inflammation and cognitive function in the general populations but have not yet been evaluated in BCS experiencing cognitive changes. Next, the model includes a biological factor, inflammation, which is a mediator by which the individual, psychosocial, and behavioral factors impact cognitive function, the health outcome. The psychosocial, behavioral, and biological factors are all independent predictors of the

Figure 1.1 Biobehavioral Conceptual Model

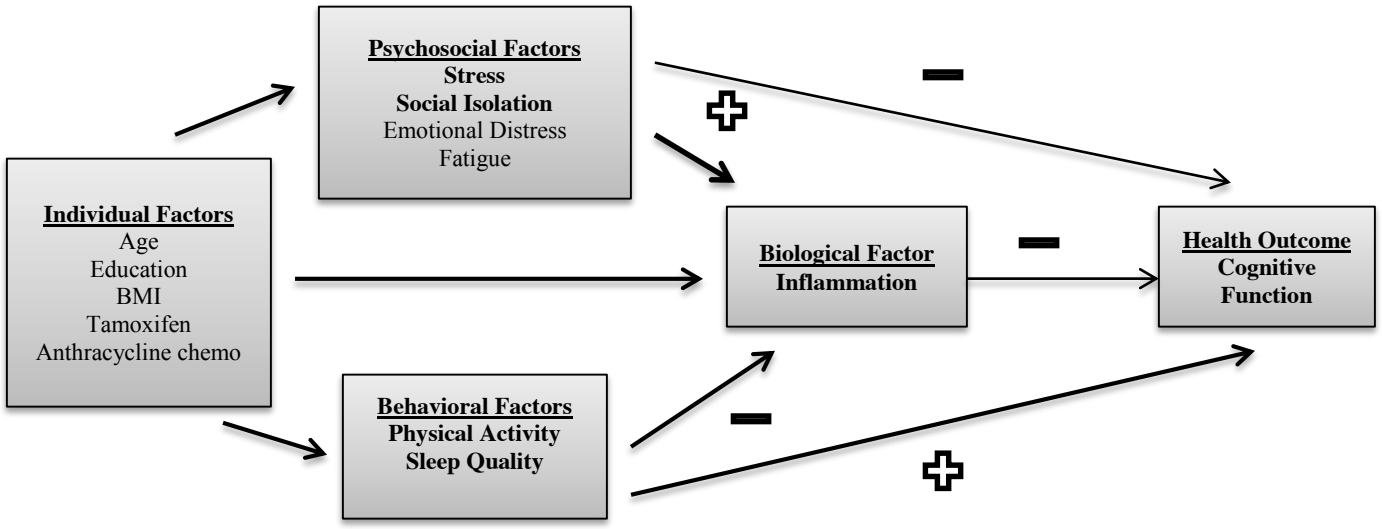

Figure 1.1. Conceptual model for the study adapted from Kang et al.'s (2010) Expanded Biobehavioral Interaction Model. Variables of interest are bolded, unbolded variables in the model are being measured for use as potential covariates and to describe the sample.

health outcome; however, the model assumes that these factors can occur simultaneously and conceptualizes that the predictor variables (individual, psychosocial, and behavioral) can be interrelated. This model provides a framework for exploring the impact of factors other than individual factors on inflammation and cognitive function in BCS following chemotherapy and will be adapted and used in this study.

PURPOSE OF THE STUDY

The purpose of this study was to identify modifiable psychosocial and behavioral factors that may contribute to cognitive function both directly and indirectly through biological factors (inflammatory markers) in 80 BCS (ages 21 to 65) six months to ten years after chemotherapy. The specific aims and hypotheses are:

HYPOTHESES

The specific hypotheses of the research aims were as follows:

Aim 1: To assess the impact of psychosocial (stress, social isolation) and behavioral (physical activity, sleep quality) factors on inflammatory markers (IL-6, TNF-α).

Hypothesis 1.1: Higher levels of stress and social isolation will predict higher levels of IL-6 and TNF-α.

Hypothesis 1.2: Higher levels of physical activity and sleep quality will predict lower levels of IL-6 and TNF-α.

Aim 2: To assess the impact of inflammatory markers on cognitive function (memory, attention, processing speed, executive function, perceived cognitive function).

Hypothesis 2.1: Higher levels of IL-6 and TNF-α will predict lower levels of cognitive function.

Aim 3 (exploratory): To explore direct and indirect effects (through inflammatory mediators IL-6 and TNF-α) of psychosocial and behavioral factors on cognitive function.

CONCEPTUAL AND OPERATIONAL DEFINITIONS

Individual Factors

Age

Theoretical Definition: Age is the length of time a person has been alive on the earth.

Operational Definition: Age was measured using participants' date of birth as a self-report question on the Demographic and Treatment Form.

Education

Theoretical Definition: Education is the process of learning under the guidance of educators (Wikipedia, 2016).

Operational Definition: Education was operationalized as number of years spent in formal education and highest degree earned as a self-report question on the Demographic and Treatment Form.

BMI

Theoretical Definition: Body mass index (BMI) is a measure of body fat in adults (Harvard Public Health, 2015)

Operational Definition: BMI is body fat calculated by a persons' height and weight— normal weight is 18.5 to 24.9 kg/m^2; 25.0 to 29.9 kg/m^2 is overweight (CDC, 2012). BMI was based on weight in kilograms and height in cm. Height was measured to the nearest 0.5 cm with participants' back to the wall, without shoes, looking straight ahead. Participants' were weighed with a standing lever scale to the nearest 100 gram, wearing no shoes and light clothing.

Tamoxifen use

Theoretical Definition: Tamoxifen is a selective endocrine receptor modulator— an oral medication used for treatment of hormone receptor (positive) breast cancer for

women who are premenopausal (Burstein et al., 2014). Tamoxifen use has been identified as a risk factor for developing cognitive dysfunction following breast cancer (Janelsins et al., 2012; Jim et al., 2012; Schilder et al., 2009).

Operational Definition: Self-report of Tamoxifen use on the Demographic and Treatment Form was operationalized by asking whether participants are currently taking or have ever taken tamoxifen.

History of Anthracycline Chemotherapy

Theoretical Definition: Anthracycline is an anthracycline topoisomerase inhibitor medication that is given intravenously and is approved for the use of adjuvant therapy for breast cancer that has spread to the lymph nodes after surgery ("Anthracycline Hydrochloride", 2014). Anthracycline has been identified as a risk factor for developing cognitive dysfunction following breast cancer (Andreano, Waisman, Donley, & Cahill, 2012; Minisini et al., 2004; Schagen, Boogerd, Muller, Dam, & Mellenbergh, 2006; Wefel, Witgert, & Meyers, 2008).

Operational Definition: Self-report of anthracycline chemotherapy use on the Demographic and Treatment Form was operationalized by asking whether participants are currently taking or have ever being treated with anthracycline chemotherapy.

Psychosocial Factors

Psychological Stress

Theoretical Definition: Lazarus & Folkman (1984) describe psychological stress as "a relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being" (p. 21).

Operational Definition: Stress was operationalized as perceived psychological stress and measured using the Perceived Stress Scale, a 10-item scale measuring the

degree that life circumstances are appraised as having been stressful in the previous 4 weeks (Golden-Kreutz, Browne, Frierson, & Andersen, 2004).

Perceived Social Isolation

Theoretical Definition: Conceptually, social isolation is comprised of objective social isolation (in regards to a persons' social network) and perceived social isolation (often referred to as loneliness). This study is focused on perceived social isolation (or loneliness) defined as "subjectively experienced, aversive emotional state resulting from the perception of unfulfilled personal and social needs" (Boss, Kang, & Branson, 2015). Perceived social isolation, is more closely related to quality rather than quantity of social interactions, (Cacioppo & Hawkley, 2009).

Operational Definition: Perceived social isolation was operationalized as loneliness and measured using the UCLA Loneliness Scale- Revised (Russel, 1996).

Emotional Distress

Theoretical Definition: The emotional state of an individual in response to a stressor that is harmful and manifests often as changes in mood, specifically, symptoms of anxiety or depression (Ridner, 2004)

Operational Definition: Emotional distress was operationalized as perceived feelings of depression and anxiety and measured using the PROMIS emotional distress scales (PROMIS Item Bank v1.0 – Emotional Distress – Depression–Short Form 8a; PROMIS Item Bank v1.0 – Emotional Distress – Anxiety – Short Form 8a).

Fatigue

Theoretical Definition: "A subjective sensation of generalized tiredness and exhaustion" (Ream & Richardson, 1996, p. 522). Furthermore, fatigue is a whole body experience, and typically a negative experience.

Operational Definition: Fatigue was operationalized as perceived feelings of tiredness and measured using the PROMIS fatigue scale (PROMIS Item Bank v1.0 – Fatigue – Short Form 8a).

Behavioral Factors

Physical Activity

Theoretical Definition: Physical activity is conceptually "any bodily movement produced by skeletal muscles that results in energy expenditure"(Caspersen, Powell, & Christenson, 1985 p. 128).

Operational Definition: Physical activity was operationalized by measuring self-reported recall of the frequency of various forms of physical activity (job related, transportation, household, recreation /leisure time, time spent sitting/sedentary time) in the last 7 days using the International Physical Activity Questionnaire (IPAQ) long version (Craig et al., 2003).

Sleep Quality

Theoretical Definition: Sleep quality has been conceptually defined as perception of sleep, actual number of hours spent sleeping, time spent trying to fall asleep. Sleep quality and daytime sleepiness can have a substantial impact on daytime functioning, including cognitive functioning (Chiu & Chao, 2010).

Operational Definition: Operational definition of sleep quality for this study is subjective reports of sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction and was measured with the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Additionally, the operational definition includes daytime sleepiness and was measured using the Epworth Daytime Sleepiness Scale (Johns, 1991).

Biological Factors

TNF- α

Theoretical Definition: Tumor necrosis factor alpha (TNF- α) is a cytokine produced by many cell types in the body including macrophages and is recognized as a defense factor that affects malignant and normal cells and is part of inflammatory cascades (Yamazaki, 1994).

Operational Definition: TNF-α was assessed from serum using a quantitative sandwich enzyme immunoassay technique according to the manufacturer's protocols (EMD Millipore; Darmstadt, Germany).

IL-6

Theoretical Definition. Interleukin-6 (IL-6) is a multifunctional cytokine that plays an important role in immune response, inflammation, and hematopoiesis (Chen, 2012).

Operational Definition. IL-6 was assessed from serum using a quantitative sandwich enzyme immunoassay technique according to the manufacturer's protocols (EMD Millipore; Darmstadt, Germany).

Cognitive Function

Theoretical Definition: Broadly speaking, cognition refers to the process of knowing that arises from awareness, perception, and reasoning (Gazzaniga, Ivry, & Mangun, 2014). Perceived cognitive function, or meta cognition, is defined as one's knowledge about knowing, or thinking about thinking (Hussain, 2015). Cognitive performance refers to how an individual behaves or "performs" under the conditions of a NP test administered by a trained professional (Hodgeson et al. 2012).

Operational Definition (s): Perceived cognitive function was operationalized as a person's perceptions of their cognitive impairments, the influence or impairments on

daily life, if others notice their cognitive changes, and how they perceive their cognitive abilities. Perceived cognitive function was measured using the Functional Assessment of Cancer Therapy-Cognitive Function Instrument version 3 (FACT-Cog; Wagner, Sweet, Butt, Lai, & Cella, 2009). Objective cognitive performance was operationalized as performance of cognitive tasks attention, verbal memory, processing speed, cognitive flexibility, executive function and measured using validated NP measures: the HVLT-R (a measure of verbal memory; Benedict, Schretlen, Groninger, & Brandt, 1998), the Trail Making Test (a measure of processing speed, executive function, attention, and cognitive flexibility; Tombaugh, 2004), and the Controlled Oral Word Association Test (a measure of verbal fluency and word finding; Wefel, Vardy, Ahles, & Schagen, 2011).

ASSUMPTIONS

The assumptions of the present study include:

1. Participants provided truthful and accurate answers to questions regarding breast cancer history and self-report measures.
2. The phenomenon "cognitive function" is comprised of both objective cognitive performance and perceived cognitive function.
3. Linear relationships exist between the study variables.

LIMITATIONS

Potential limitations of the current study include:

1. The design is cross sectional; therefore, causality cannot be assumed.
2. Results from the study cannot be generalized beyond breast cancer survivors (stage I-III) treated with chemotherapy six months to 10 years after primary treatment.

3. Participants in this study may not reflect other breast cancer survivors who may not be willing or able to participate in this study or live geographical areas outside of Central Texas.
4. Self-report measures can be influenced by response bias.
5. NP evaluation may not be sensitive enough to capture survivors' problems with cognitive function.
6. Biomarkers chosen for analysis here may not adequately capture the inflammatory response related to cognitive functioning

SUMMARY

This chapter discussed the background and significance of problems with cognitive function following breast cancer chemotherapy. The primary purpose of this study was to identify modifiable psychosocial and behavioral factors that may contribute to cognitive function both directly and indirectly through biological factors (inflammatory markers) in 80 BCS (ages 21 to 65) six months to 10 years after chemotherapy. A biobehavioral framework proposed by Kang et al. (2010) guided this study to simultaneously evaluate the direct and indirect effects (through biological mediators) of individual, psychosocial, behavioral factors on cognitive function in breast cancer survivors. Findings from this study advance the science in the direction of theoretically based translational research—building on previous research that has identified factors that increase survivors' vulnerability to problems with cognitive function, and identifying modifiable factors that may also contribute to inflammation and cognitive function in BCS. This study provides foundational evidence for future prospective research studies and targets for behavioral interventions.

The study is significant because it (1) fills a gap in the literature by providing knowledge on inflammation and cognitive function 6 months to ten years after breast

cancer chemotherapy; (2) using a biobehavioral model to simultaneously evaluate modifiable psychosocial and behavioral factors that may be contributing to inflammation and cognitive function in BCS; and (3) provides initial evidence for needed future prospective and translational studies to improve cognitive function in BCS.

Chapter 2: Review of the Literature

This chapter presents a review of the literature relevant to the topic of modifiable factors that may contribute to cognitive function following breast cancer chemotherapy. The chapter begins with an overview of breast cancer and the late effects of breast cancer treatment. Next, the cognitive changes associated with breast cancer treatment are discussed including the prevalence, effects on daily functioning, along with identified risk factors and likely contributing factors. Possible etiological mechanisms of cognitive changes after breast cancer treatment are presented with an emphasis on recent research suggesting the role of inflammation. The chapter continues with several systematic review of modifiable behavioral and psychosocial factors that may contribute to both inflammation and cognitive function in breast cancer survivors (BCS)— the topic of this study. Systematic reviews were conducted to fully understand the relationships between the variables of interest (stress, social isolation, physical activity, and sleep quality) and both inflammation and cognitive function, especially what is known in oncology populations.

BREAST CANCER OVERVIEW

Breast cancer accounts for 29% of newly diagnosed cancers in the United States. Seventy-nine percent of new breast cancer cases occur in women 50 years of age or older. Women in the U.S. have a 1 in 8 lifetime risk of being diagnosed with breast cancer. The incidence of breast cancer diagnoses is highest in non-Hispanic whites; however, African American women have the highest mortality rates at all ages (American Cancer Society, 2013).

Breast cancer originates in breast tissue and is characterized as either in situ (originating in the cells lining the breast ducts), or invasive, (cancer cells have migrated

out of the ductal walls into the breast tissue, also known as *infiltrating*). The majority of breast cancer diagnoses are invasive breast cancer, and in 2013 there were an estimated 232,340 new cases of invasive breast cancer in the U.S. Two staging systems exist for cancer— the TNM (tumor, nodes, metastasis) classification and the Surveillance, Epidemiology and End Results (SEER) summary staging system. The SEER staging system is a simplified system and used for cancer registry reporting. According to the SEER system, local stage refers to those tumors contained to the breast (corresponding to stage 1 or II in the TNM system); regional stage refers to tumors that have spread to surrounding tissue including lymph nodes (corresponding to stage II or III depending on the size); and distant stage refers to tumors that have spread to distant organs or bones (corresponding with stages IIIc and IV; American Cancer Society, 2013).

Breast cancer screening and prevention includes self-breast exam, mammography, clinical breast examination, and magnetic resonance imaging. Clinical breast examinations are recommended for average-risk women in their 20's and 30's every three years. The American Cancer Society recommends that 1) women ages 40 to 44 should have a choice to receive an annual mammography; 2) all women should receive an annual mammography screening and clinical breast examinations from ages 45 to 54; and 3) women 55 and older should switch to a mammography every other year (American Cancer Society, 2015). Early detection of breast cancer with mammography reduces the risk of breast cancer death by one-third and leads to increased treatment options. Women are utilizing breast cancer screening tools now more than ever before. In 2010, a national survey was conducted and it was reported that 67% of women 40 years of age or older had a mammogram in the previous two years (an increase from 29% in 1987; American Cancer Society, 2013).

Breast cancer treatment depends on stage and biological characteristics of the cancer and includes surgery, radiation therapy, and systematic therapy (chemotherapy, hormone therapy, and targeted therapy). Systemic therapy is also referred to as adjuvant treatment. Most women will receive surgery combined with another treatment modality or modalities. Advancements in breast cancer treatments have greatly decreased mortality rates and a breast cancer survivor cohort is growing. In 2012, more than 2.9 million U.S. women had a history of breast cancer. For local disease the five year survival rate is 99%, for regional disease it is 84%, and for distant stage disease 24% (American Cancer Society, 2013). These statistics highlight the importance of understanding and meeting the unique needs of cancer survivors.

SUMMARY

Breast cancer is the most common cancer, affecting women in the United States. Improvements in cancer screening, diagnosis, and treatment are contributing to an increasing number of cancer survivors with their own unique health needs.

LATE AND LONG TERM EFFECTS OF BREAST CANCER TREATMENT

The advances in breast cancer treatments are not without unintended consequences that include long-term and/or late effects of treatment. “Long-term effects” of treatment refer to adverse symptoms that appear during treatment and persist months or years after treatment stops. “Late effects” of treatment refer to symptoms that appear secondary to cancer treatments 12 months or more after curative treatment ends (Crist, 2013). Most BCS will ultimately face physical, psychological, and practical complications for months to years after treatment ends (Hewitt, Greenfield& Stovall, 2005) including psychosocial distress, lymphedema, estrogen deprivation, insomnia, fatigue, and cognitive dysfunction (Pinto & de Azambuja, 2011). An estimated 75% of cancer survivors experience physical and psychosocial late effects of treatment (Ganz,

2005) that can negatively impact daily functioning and social role performance (the ability to act in socially defined roles and complete the tasks appropriate within one's sociocultural and physical environment; Verbrugge & Jette, 1994), such as returning to work or sustaining employment (Crist, 2013; Hewitt et al., 2005, Ness et al. 2013).

COGNITIVE FUNCTION FOLLOWING BREAST CANCER

One of cancer's most distressing (Boykoff et al., 2009), feared (Ganz et al., 2013), and prevalent (Janelsins et al., 2014) long-term/late effect of treatment is cognitive dysfunction. Most often cognitive dysfunction occurs in the domains of memory, attention, processing speed, and executive function (Janelsins et al., 2014; Wefel & Schagen, 2012). Collectively, dysfunction in these domains is referred to as cancer-related cognitive impairments (CRCI). Twenty years of research (primarily in breast cancer patients) has consistently confirmed relationships between CRCI and adjuvant cancer treatment, namely chemotherapy (Hodgson, Hutchinson, Wilson, & Nettelbeck, 2013; Jim et al., 2012; Saykin et al., 2013).

The definitions of "cognitive impairment" and "cognitive decline" are variable across studies that utilize NP assessment. Cognitive impairment is typically defined as two standard deviations below a healthy control or published norm. Cognitive decline refers to a one to two standard deviation change from pre-treatment to post-treatment (Ono et al., 2015) in prospective studies. It should be noted that, "There is no widely accepted statistical convention or cut-off in determining clinically significant declines or impairments in cognitive functioning." (Ono et al., 2015, p. 2).

Estimates of the prevalence of CRCI vary; however, most recent longitudinal research studies utilizing NP assessments indicate that up to 30%-40% of patients experience CRCI prior to starting adjuvant treatment; 75% experience CRCI during adjuvant treatment; and 35%-60% experience CRCI for months to years following the

end of treatment (Janelsins et al., 2014; Wefel, Kesler, Noll, & Schagen, 2015). Long-term CRCI has been reported in BCS seven to nine years after end of treatment (Amidi et al., 2015) and in some cases up to 20 years later (Koppelmans et al., 2012). When self-report measures are used to evaluate cognitive function in survivors, prevalence rates are much higher— up to 90% (Pullens, De Vries, Roukema, 2010). Self-reported cognitive dysfunction is more strongly correlated with fatigue and affective symptoms such as anxiety, depression, and distress than cognitive performance measures (Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012; Pullens et al., 2010; Wefel et al., 2015).

BCS's neurocognitive test performance usually fall into the range "mild cognitive impairment"; although, survivors often report significant impact on functioning (Hutchinson et al., 2012; Wefel et al., 2015). The evidence surrounding associations between subjective measures and measures of cognitive performance is inconclusive, suggesting that self-report and objective measures capture different aspects of CRCI and both should be utilized in research to capture the phenomenon of CRCI (Ganz et al., 2013; Pullens et al., 2010).

CRCI usually presents within six months of initiating chemotherapy, with full or partial recovery one year after chemotherapy ends (Kesler et al., 2013). The pattern of CRCI is unique to the individual and can vary in terms of the domains affected, severity of dysfunction, and duration of cognitive changes (Janelsins et al., 2014). The "severity" of this problem has been estimated statistically with effect sizes that range from 0.3 to 0.5 when calculated using standardized mean differences of the means and standard deviations reported for each NP test result (O'Farrell, MacKenzie, & Collins, 2012).

A recent review article by Ono and colleagues (2015) reported that, in general, patients exposed to chemotherapy performed worse than controls on general cognitive

tasks in cross sectional studies using a random effects model (*d*=-0.14, 95% *CI* from -0.14 to -0.11). In prospective studies, chemotherapy patients showed improved overall cognitive functioning from their pre-chemotherapy to post chemotherapy assessments (*d*=0.11 95% *CI* from 0.09 to 0.14). However, when weighted grand mean scores for the eight individual cognitive domains were calculated (attention, executive function, language, long-term memory, short-term memory, motor function, processing speed, and visuospatial function), larger effect sizes were found in both cross sectional and longitudinal studies (weighted mean effect sizes using random effects models ranged from *d*=-0.04 to -0.25). The largest effect sizes were found in processing speed, executive function, and attention using random effects models (*d*= -0.25 and -0.19, -0.16, $p<.05$) indicating that chemotherapy patients experienced impairments in these domains compared to controls in cross sectional studies. Effect sizes ranged from *d*= -0.29 to *d*= 0.41 across cognitive domains in longitudinal studies using random effects models. The only significant effect was found for long-term memory (*d*=0.41) indicating that chemotherapy patients improved in long-term memory when reassessed after treatment. These differences in magnitude between general cognitive impairments and specific cognitive domains suggest that chemotherapy related cognitive changes are likely specific rather than generalized (Ono et al., 2015, p. 8).

Structural and functional neuroimaging techniques have been used to investigate the neural substrates of CRCI. Researchers consistently report subtle and diffuse brain changes in survivors exposed to chemotherapy compared to healthy controls or cancer survivors not exposed to chemotherapy. These diffuse brain changes include decreased grey matter volume and white matter atrophy (Ahles, Root & Ryan, 2012, deRuiter & Schagen, 2013; Kesler, 2014; McDonald, Conroy, Ahles, West, & Saykin, 2012). Decreased grey matter volume appears to be most pronounced in the prefrontal and

temporal lobes (Janelsins et al., 2014). Diffusion tensor imaging has showed decreased white matter integrity from 12 months to 20 years post treatment in survivors compared to healthy controls and in some cases compared to non-chemotherapy treated survivors (Deprez, Billiet, Sunaert, & Leemans, 2013). A recent study by Kesler et al. (2016) reported that BCSs treated with anthracycline-based chemotherapies demonstrated less efficient brain connectivity than those treated with non-anthracycline based chemotherapies using resting state fMRI imaging techniques. Other types of imaging methods including functional magnetic resonance imaging (fMRI), spectroscopy, and positron emission tomography (PET) have shown altered neurochemistry, activation patterns, and brain metabolism in survivors compared to healthy controls (McDonald & Saykin, 2013; Saykin et al., 2013; Janelsins et al., 2014, Conroy et al., 2013).

Importantly, even subtle impairments, indicated by small statistical effect sizes can have profound effects on daily life (Wefel et al., 2015). CRCI is a major concern because this set of problems can interfere with medication adherence, negatively affect quality of life, impair productivity, and reduce abilities to return to work (Janelsins et al., 2014). Our previous study noted BCS descriptions of psychological distress, embarrassment, and guilt associated with CRCI (Becker, Henneghan & Mikan, 2015). For these reasons, efforts have been made to evaluate and test interventions including medications, cognitive behavioral therapies, cognitive training, and physical activity to ameliorate symptoms associated with CRCI, and results have been mixed (Craig, Monk, Farley, & Chase, 2014; Janelsins et al., 2014; Wefel et al., 2015). Improvements in objective measures of cognitive function and perceived cognitive function have been reported in studies of several behavioral interventions (Alvarez, Meyer, Granoff, & Lundy, 2013; Becker et al., 2015; Cherrier et al., 2013; Ercoli et al., 2013; Ferguson et al., 2012; Oh et al., 2012). Three studies have utilized computerized cognitive training

and reported significant improvements in executive function, verbal fluency, processing speed (Kesler et al., 2013), and verbal memory (Von ah et al., 2012) along with self-report measures of cognition (Kesler et al., 2013; Von ah et al., 2012). Most of the studies evaluating pharmaceutical interventions including donepezil, modafinil, and epoetin have not found significant improvements in cognitive function (Craig et al., 2014), with the exception of two studies of modafinil that reported improved memory, attention (Kohli et al., 2009), and psychomotor speed (Lundorff, Jonsson, & Sjogren, 2009). Several studies have evaluated the effect of physical activity interventions, albeit non-aerobic physical activity, on cognitive function in BCS and reported improvements in self-reported cognitive function, quality of life, and psychological symptoms (Alvarez et al., 2013; Janelsins et al., 2012; Oh et al., 2012; Reid-Arndt & Cox, 2012).

SUMMARY

Taken together, approximately one third of BCS who undergo chemotherapy as part of their treatment will experience long term or late cognitive changes that are distressing and can negatively affect daily functioning and quality of life. Imaging studies have consistently elucidated structural and functional brain changes in BCS treated with chemotherapy compared to those not treated with chemotherapy and to controls. Efforts have been made to improve cognitive functioning in BCS with modest results, likely because the exact etiology of this phenomenon is not completely understood and the cause of CRCI is likely multifactorial. A better understanding of the mechanism of CRCI will aid in finding effective treatments for this problem.

PROPOSED MECHANISMS FOR CRCI

Several mechanisms have been proposed in the literature to explain the manifestation of CRCI. These include direct effects of chemotherapy on the central nervous system; indirect effects of chemotherapy on the central nervous system;

processes related to the cancer pathology, and processes related to hormone imbalances (stress-related hormones and estrogen) (Craig et al., 2014; Wefel et al., 2015).

Direct Effects

Chemotherapy targets rapidly dividing cells in the body; therefore, it can affect healthy cells and lead to many unwanted side effects. Several chemotherapies have been shown to cause damage to the central nervous system; in fact, it has been demonstrated that some are more toxic to brain cells than to cancer cells (Dietrich, Han, Yang, Y., Mayer-Pröschel, & Noble, 2006; Wefel et al., 2015). In animal models, the direct effects of chemotherapies on the central nervous system appear clear (Seigers, & Fardell, 2011) and include hippocampal toxicity (Dietrich et al., 2015), white matter degradation, and neuroinflammation (Seigers, & Fardell, 2011). It is unknown how these animal models translate to the human brain (Dietrich, Prust, & Kaiser, 2015). Clinical data support animal models and also suggests structural and functional brain changes associated with chemotherapy treatment including hippocampal volume reduction and altered patterns of neural activation (Dietrich et al., 2015); however, more clinical research is needed to yield conclusive findings (Craig et al., 2014).

Indirect Effects

Another proposed mechanism of CRCI is the indirect effects of chemotherapy on processes in the body such as inducing pro-inflammatory cascades. These cascades can lead to prolonged cytokine activation and subsequent production of reactive oxygen species (ROS). ROS have adverse effects on the brain via inflammatory mechanisms that will be discussed in detail in the following section titled "Inflammation and CRCI in BCS". Chemotherapy toxicity can result in an imbalanced oxidative stress load from the production of ROS, that leads to DNA mutations and further ROS production (a vicious cycle), that results in high oxidative stress, damaged neurons, and cognitive impairments

(Craig et al., 2014; Seigers & Fardell, 2011; Wefel et al., 2015). Oxidative damage has already been associated with other neurodegenerative diseases such as Alzheimer's, Parkinson's disease, and mild cognitive impairment (Walker, Drew, Antoon, Kalueff, & Beckman, 2012). Moreover, high levels of oxidative stress and DNA damage may be even more detrimental to cancer patients and survivors who likely already have decreased DNA repair abilities (Walker et al., 2012).

Cancer-related Mechanisms

Changes in cognitive function prior to initiation of chemotherapy led scientists to theorize that physiological processes due to the cancer itself could lead to CRCI. For instance, the body has inflammatory responses to cancer that can trigger neurotoxic pro-inflammatory cascades (Wefel et al., 2015). Additionally, relationships between greater disease severity and more cognitive problems have been reported (Ahles, et al., 2008; Kesler, Kent, & O'Hara, 2011). It has been demonstrated that some tumors interfere with protective immune responses to cancer that can lead to higher levels of inflammation that are sustained over time (Seruga, Zhang, Bernstein, & Tannock, 2008; Whiteside, 2006).

Hormonal Changes

Cancer patients and survivors are subject to high levels of psychological stress that can interfere with hypothalamic-pituitary-adrenal (HPA) axis function and result in irregular levels of circulating glucocorticoids. It is documented that glucocorticoids can trigger damage to areas of the brain (Seigers & Fardell, 2011). High levels of stress can also over tax the HPA axis and result in sub optimal levels of glucocorticoids resulting in dysregulation of cytokines in the body that can lead to cognitive dysfunction (Kesler et al., 2013). Similarly, sex hormones have been linked to cognitive functioning. Estrogen is thought to be neuro-protective— playing a role in both neurotransmitter production and relieving oxidative stress (Walker et al., 2012). There are estrogen receptors in the

brain—in the hippocampus, cerebral cortex, and frontal lobe. In animal models, low estrogen can result in cognitive impairments (Craig et al., 2014); however, the action of estrogen in the human brain appears to be more complex and is not completely understood (Walker et al., 2012).

Inflammation and CRCI in BCS

A leading candidate mechanism of CRCI is the indirect neurotoxic effect of chemotherapy resulting in inflammation that leads to cognitive impairments (Saykin & Ahles, 2007; Janelsins et al., 2011; Vardy, 2009). Both cancer and cancer treatment have been shown to elevate peripheral pro-inflammatory markers, including cytokines, in women with breast cancer (Seruga et al., 2008; Kesler et al., 2013). A summary of the research supporting the connection between inflammation and CRCI in oncology populations can be found in Table 2.1. Cytokines are "polypeptides produced principally inflammation and immune responses" (Walker et al., 2012, p. 142). In the brain, cytokines have also been shown to play a role in neural repair and modulate neurotransmission (Walker et al., 2012). A growing body of animal and human research indicates that high levels of circulating pro-inflammatory markers can access the brain and cause neurotoxic damage, resulting in a sequelae of behavioral symptoms including depression, sleep disturbance, fatigue, and cognitive dysfunction (Ahles et al., 2014; Cheung et al., 2014; Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008; Pomykala et al., 2013; Saykin et al., 2013; Seruga et al., 2008). Prolonged exposure to inflammatory cytokines can have degenerative effects on the human body including neurodegeneration. Inflammatory cytokines have been investigated in relation to Alzheimer's disease and mild cognitive impairment, and literature supports links between low-grade systemic inflammation and cognitive impairments in adults (Nascimento et al., 2014).

Table 2.1

Inflammation and CRCI in Oncology populations

First Author, Year	Objective	Sample	Design	Inflammatory variable	Cognitive Variable	Key Findings
Andreano, 2012	To assess the influence of glucocorticoid and ovarian disruption on cognitive function in BCS	BC patients on Lupron to prevent recurrence (n=20) Stage unspecified 70% chemo Controls (n= 20)	Experimental T1 (anytime during Lupron treatment) T2 (1 week after T1)	Cortisol (*salivary cortisol ELISA*	Immediate & Delayed Memory (NP): *WMS III subtests- verbal paired associates; logical memory- Story A [emotionally charged story] and Story B [weather report)]*	Controls (T2) recall for story A was significantly positively correlated with salivary cortisol levels (r=.54, p<.05, df=9), No significant correlations between cortisol and recall in the breast cancer at any time-suggesting reduced glucocorticoid responsiveness
Cheung, 2015	To evaluate the effect of chemo induced inflammatory response on breast cancer patients' cognitive function	BC patients (n=99) Mean age 50.5 (8.4) Stage I-III Anthracycline Chemo (70.7%)	Multi-Centered Prospective Cohort T1 (before chemo initiation) T2 (6 weeks after T1) T3 (12 weeks after T1)	Cytokines (*immunoassay kit for interleukins [IL-1β; IL-2; IL-4; IL-6; IL-8; IL-10]; granulocyte-macrophage colony stimulating factor [GM-CSF]; interferon [IFN-γ]*	(NP) *Cognitive Stability Index (Headminder)* Perceived cognitive function (*FACT-Cog version 3)*	IL-1β was associated with 0.78 decrease in response performance (p=.023) Higher concentration of IL-4 was associated with better response speed performance (p= .022) Higher concentrations of IL-1β and IL-6 were associated with more perceived cognitive disturbances (p=.018; p =.001) Every unit increase of IL-4 was associated with 0.95 increase in FACT-Cog total score (p=.022)
Conroy, 2013	To examine the association of perceived cognitive impairments with	BC survivors 3-10 years after chemo (n=24) Mean age 57.8 (9.6)	Multimodal MRI (imaging) study	Oxidative damage (*modified alkaline Comet assay of oxidative DNA damage)*	Perceived Cognitive Function (*MASQ; FACT-Cog)*	No significant relationships between oxidative damage and perceived cognitive impairments (MASQ, FACT-Cog) Increased oxidative damage was related to

Table 2.1 (continued)

	gray matter density and working memory-related MRI brain activation in breast cancer survivors	Stage I-IIIb Doxorubicin-based chemo Age & education matched controls (n=23)				lower gray matter density (r= -.5, p=.011) in breast cancer survivors
Ganz, 2013	To determine whether or not there is a significant relationship between recent chemo exposure in women with early stage breast cancer and pro-inflammatory cytokines and how these markers interact with other behavioral symptoms	Early Stage BCS (n=49) Age 49.9 (8.5) 92% Stage I-II Anthracycline Chemo (29%)	Observational Cohort Study T1: 0-3 months post primary treatment T2: 6 months later T3: 12 months later	Cytokine **(***ELISA sTNF-RII)*	Memory (*SMQ)*	At T1 significant negative correlation between sTNF-RII and SMQ (r=-.21, p=.05) controlling for age, BMI, radiation and depression Significant negative correlation between change in SMQ and change in sTNF-RII from T1 to T3 (r=-.34, p=.04)
Janelsins, 2012	To compare levels of IL-6, IL-8, and MCP-1 in patients receiving doxorubicin-based chemo with levels in those receiving a combination of CMF chemo and their relationships with cognitive complaints	BC patients receiving chemo: Group 1 (n= 27, age 52.85 (8.64); AC/CAF chemo) Group 2 (n= 27, age 50.18 (9.62), CMF chemo) Stage unspecified	Secondary Analysis of Randomized Control Trial T1: 1st 0-2 cycles of chemo T4: after 2 more cycles of chemo	Cytokines *(ELISA-IL-6, IL-8, monocyte chemo-attractant protein)*	Perceived global cognition (Fatigue Symptom Checklist -5 yes/no questions heavy headed, muddled thoughts, difficulty thinking, difficulty with concentration, forgetfulness)	In the AC/CAF group: Changes in MCP-1 from T1 to T2 significantly correlated with difficulty concentrating (r = -.498, p <.05) and forgetfulness *(*r=-.466, p<.05) Both IL-8 and IL-6 were positively correlated with all the items (p=NS) In the CMF group: IL-6 was negatively correlated with all 5 items (p=NS) IL-8 was positively correlated with all but difficulty thinking (p=NS) MCP was positively correlated with all items except heavy headed (p=NS)
Kesler,	To investigate the	BCS (n=20)	Cross-sectional	Cytokines **(***IL- 6,*	Perceived Memory	A significant interaction between IL-6 and

Table 2.1 (continued)

2013	relationships between hippocampal structure, verbal memory performance, and peripheral cytokines in breast cancer survivors	Mean age 54.6 (6.5) Stage 2.12 (.72) 100% chemo		*IL-8, IL-1-, IL_12, IL-1-beta, IL-β, IFNγ, TNF-α)*	(*MMQ)* Memory performance (*HVLT-R)*	TNFα on the HVLT-R was reported in the chemo treated breast cancer survivors (β= -2.46, p =.006) MMQ not associated with cytokines
Pomykala, 2013	To examine relationships following adjuvant chemo between pro-inflammatory cytokines, regional cerebral metabolism and cognitive complaints in early stage breast cancer patients	BCS (n= 33) Stage 0-IIIA (59% Stage 2) 69.6 % chemo, 35% anthracycline	Observational Cohort Study Baseline: 0-3 months post primary treatment T2: 6 months later T3: 12 months later	Cytokines (*interleukin 6 soluble TNF receptor type II)*	Cognitive Complaints in memory, High-level Cognition, Sensory Motor, Language/ Communication (*PAOFI)*	At baseline-significant positive correlation between total severity scores for PAOFI memory subscale and IL-6 levels (p= .0287, n=32)

Note. Outcomes**:** SR, Self-rated; NP, neuropsychological test performance Self-Report Measures. AFI, Attentional Function Index; BAI, Beck Anxiety Inventory; BRIEF, Behavioral Rating Inventory of Executive Function; CSC-W59, Cognitive Symptom Checklist Work-59; FACT-COG, Functional Assessment of Cancer Treatment Cognition; EORTC-CFS, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 version 3.0; FEDA, Questionnaire of Experienced Deficits of Attention; GHQ-12, General Health Questionnaire- 12; GSDS, General Sleep Disturbance Scale; GLT-EQ, Godin Leisure Time- Exercise Questionnaire; HADS, Hospital Anxiety Depression Scale; PSQI, Pittsburgh Sleep Quality Index; MASQ, Multiple Ability Self-Report Questionnaire; MMQ, Memory Questionnaire Ability Scale; PANAS, Positive and Negative Affect Schedule; PAOFI, Patient's Complaints of Own Functioning Inventory; SMQ, Squire Memory Questionnaire; TEA, Test of Everyday Attention Neuropsychological Tests. COWAT; Controlled Oral Word Association Test; HVLT-R, Hopkins Verbal Learning Test Revised; RCFT; Rey Complex Figure Test; WAIS-IV, Wechsler Adult Intelligence Scale 4th edition; WCST, Wisconsin Card Sorting Test*;* WMS III, Wechsler Memory Scale III.

Elevated levels of IL-6 and TNF-α have been found in mild cognitively impaired elderly compared to non-impaired controls (Nascinmento et al., 2014). TNF-α has been associated with demyelination in the brain and high levels of TNF-α are consistently associated with breast cancer. High levels of IL-6 have been associated with several chemotherapy agents and IL-6 has also been associated with poor executive functioning (Walker et al., 2012). Furthermore, stress elicited by cancer and cancer treatment (including chemotherapy) can disrupt the HPA axis regulation of high levels of circulating cytokines (Kesler et al., 2013) and treatments that stimulate cytokine production have been associated with cognitive deficits (Vardy, Wefel, Ahles, Tannock, & Schagen, 2008). Taken together, the evidence suggests that cytokines may mediate cognitive impairments both during and after chemotherapy (Cheung et al., 2014; Ganz et al., 2013; Kesler et al., 2013; Janelsins, Mustian, et al., 2012; Pomykala et al., 2013). Subsequently, investigators have begun to evaluate the role of inflammation in survivors' cognitive function.

Much of the research related to inflammation and cognition in BCS has evaluated pro-inflammatory biomarkers, including interleukins (IL), interferons (IFN), tumor necrosis factor (TNF), and soluble TNF receptors (sTNF-R; Cheung, 2013). Ganz et al. (2013) reported that the longitudinal decline in sTNF-RII levels was significantly correlated with fewer self-reported memory complaints in BCS who received chemotherapy (n=49: r=-.34, p=.04). Kesler et al. (2013) found a significant interaction between TNF-α and IL-6 and verbal memory performance in BCS (n=42) 4.8 ± 3.4 years post-chemotherapy suggesting that IL-6 may modulate the effects of TNF-α on verbal memory and the hippocampus following breast cancer and chemotherapy (*beta*=-2.46, p=.006). Janelsins et al. (2012) found a significant inverse relationship between monocyte chemoattractant protein-1 (MCP-1) and forgetfulness (r=-.47, p=.019) and a positive

correlation approaching significance between higher levels of IL-6 and greater difficulty concentrating (r=.38, p=.059) in breast cancer patients who received anthracycline-based chemotherapy. Finally, another study reported that higher levels of IL-1β predicted slower processing speed (p=.008), higher TNF-α predicted memory decline (p=.003), and both higher IL-4 (p=.025) and IL-8 predicted worsening attention (p=.021) in 81 breast cancer patients (Cheung et al., 2014). Only one of the aforementioned studies (Vardy, 2009); however, evaluated these relationships one or more years after chemotherapy.

Associations between inflammatory factors and neural correlates of CRCI have also been explored. Kesler et al. (2013) found that higher levels of both TNF-α and IL-6 were significant predictors of lower hippocampal volume (using MRI) in 20 BCS who received chemotherapy. Pomykala et al. (2013) reported consistent correlations between less left medial frontal and right anterior temporal cortical metabolism and higher levels of inflammatory markers (IL-1ra, sTNF-RII, CRP, IL-6) in BCS who received chemotherapy 18 months earlier (n=23) suggesting neural inefficiencies.

SUMMARY

Taken together, several mechanisms have been proposed to explain the manifestation and persistence of CRCI in BCS and research suggests a link between inflammation and cognitive changes experienced by BCS. Recent research has demonstrated relationships between higher TNF-α, higher IL-6, interactions between these two cytokines, and worse cognitive functioning and cognitive performance.

CONTRIBUTING FACTORS TO COGNITIVE FUNCTION IN BREAST CANCER SURVIVORS

Individual Factors and Cognitive Function

It is well documented that there are several predisposing or precipitating demographic, treatment, and emotional factors that contribute to CRCI in BCS. Demographic factors like older age (Ahles et al., 2012; Janelsins et al., 2014; Mandelblatt

et al., 2013; Ono et al., 2015; Wefel & Schagen, 2012), lower cognitive reserve (as estimated by either educational attainment or IQ; Ahles et al., 2010; Janelsins et al., 2012), and pre treatment menopausal status (Conroy et al., 2013) have at times been found to be risk factors for developing CRCI. At other times researchers failed to find such correlations (Ahles et al., 2010; Janelsins et al., 2014).

Certain genetic factors have been proposed as risk factors for CRCI (Ahles, et al., 2012). APOE is a glycoprotein responsible for the uptake, transport, and distribution of lipids and has been shown to play a role in neural repair and plasticity (Walker et al., 2012, p.142). In 2003, Ahles et al. established an association between apoliprotein E (APOE) E4 allelle and lower cognitive performance on memory and spatial ability tasks along with a trend towards lower performance on an executive function task. More recently, Lengacher et al. (2015) reported findings that support this association. Two studies have established associations between single nucleotide polymorphisms (SNPs) and CRCI, specifically with the SNPs: catecholo-methyltransferase (COMT; Small et al., 2011), ankyrin repeat and kinase domain containing 1 (ANKK1; Lengacher et al., 2015), methylenetetrahydrofolate reductase (MTHFR; Lengacher et al., 2015), and solute carrier family 6 member 4 (SLC6A4; Lengacher et al., 2015). In these studies, survivors who were carriers of the aforementioned SNPs performed worse than healthy controls on tests of attention, verbal fluency, and motor speed (Small et al., 2011), and had worse perceived cognitive function (Lengacher et al., 2015).

Cancer treatment factors including less time since chemotherapy, higher dose of chemotherapy, and greater number of chemotherapies and/or treatment modalities have also been associated with vulnerability to CRCI. Evidence suggests a dose response relationship between chemotherapy and CRCI. Higher doses of chemotherapy (more cycles, longer duration) have been associated with greater cognitive impairments,

decline, and structural and electrophysiological changes in breast cancer patients (O'Fardell et al., 2013). Additionally, certain types of chemotherapies (anthracycline-based and methotrexate) have been associated with higher risk of CRCI (Janelsins et al., 2012; Kesler & Blaney, 2016); however, methotrexate is not commonly used to treat breast cancer anymore. Studies with the majority of participants with a history of anthracycline chemotherapy (e.g. anthracycline) show worse cognitive performance than controls (McDonald, 2012; Kesler, 2011; Lepage, 2014). Neuroimaging studies comparing anthracycline chemotherapies to non-anthracycline show altered morphology and activation patterns in those with anthracycline chemotherapies (Koppelmans, 2013). Only one study to the author's knowledge has directly compared anthracycline-based chemotherapies to non- anthracycline chemotherapies in a clinical population on cognitive measures (kesler and blayney, 2016). Kesler & Blayney (2016) reported significantly lower verbal memory (both immediate and delayed) in those treated with anthracycline-based chemotherapy than those treated with non-anthracycline chemotherapy, but similar levels of perceived cognitive dysfunction in both groups. Janelsins et al. (2012) found differences in cytokine expressions when comparing anthracycline-based chemotherapy to non-anthracycline based chemotherapy in breast cancer patients. Hormonal treatments are another treatment factor linked to CRCI (O'Fardell et al., 2013). Tamoxifen (a selective estrogen receptor modulator) decreases the effects of estrogen in the bone and endometrium (Walker et al., 2012) and has been associated with greater cognitive impairments such as verbal memory deficits in BCS taking tamoxifen compared to BCS not taking this medication (Walker et al., 2012).

It is widely accepted that anxiety, depression, and fatigue contribute to cognitive function. For many years, the cognitive changes reported by breast cancer patients were attributed to psychological or emotional distress and treated with anti-depressants.

Anxiety, depression, and fatigue correlate with perceived cognitive dysfunction stronger than performance measures, and in some cases these factors do not correlate at all with cognitive performance (O'Fardell et al., 2013). Even though the relationships between CRCI and anxiety, depression (Asher, 2011; Poppelreuter et al., 2004; Pullens et al., 2010) and fatigue (Bower & Lamkin, 2013; Cheung, Lim, Ho, & Chan, 2013; Hodgson et al., 2013; Hutchinson et al., 2012) are clear, these factors do not completely explain why one third of survivors who undergo chemotherapy experience ongoing problems with cognitive function more than one year after treatment ends. Therefore, other factors must contribute to the manifestation of cognitive impairments and/or decline in BCS.

Of the demographic, treatment, and emotional factors discussed above, the following are being measured in this study for their potential use as covariates because they have been consistently reported in the literature as risk factors for either cognitive function or inflammation— age, education, BMI, tamoxifen use, history of anthracycline-based chemotherapy, emotional distress, and fatigue.

MODIFIABLE FACTORS

With the exception of the emotional and fatigue related factors (which are not the focus of this study), the demographic and treatment related risk factors for CRCI discussed in the previous section are largely not modifiable or unavoidable when faced with breast cancer. It is possible that other factors that *are* modifiable may contribute to cognitive function either directly or indirectly, through inflammatory mediators. For instance, stress (Aggarwal et al., 2014; Carlson, Speca, Faris, & Patel, 2007, Lupien 2005 & 2009), physical activity (Beavers, Brinkley, & Nicklas, 2010, Bherer, Erickson, & Liu-Ambrose, 2013), social isolation (Cacioppo & Hawkley, 2009; Yang, McClintock, Kozloski, 2013), and sleep (Clevenger et al., 2012; Miller et al., 2009; Sprod et al., 2010)

have been associated with inflammation and cognitive function in similar populations but have not been simultaneously evaluated in BCS.

These modifiable factors (stress, perceived social isolation, physical activity, and sleep quality) may be particularly relevant to BCS because survivors experience one and a half times more stress than the general population (Parelkar, Thompson, Kaw, Miner, & Stein, 2013). Additionally, BCS experience a unique type of loneliness following the completion of treatment termed "survivor loneliness" that encompasses a sense of loneliness in the face of mortality and invalidated, ongoing symptom burden (Rosedale, 2009). Up to 87% of cancer patients experience sleep problems that persist long after treatment ends (Palesh et al., 2012), and breast cancer patients experience insomnia more frequently than persons with other types of cancer (Caplette-Gingras, Savard, Savard, & Ivers, 2013). And finally, only 37% of BCS (*n*=2,885) are meeting physical activity guidelines (Blanchard et al., 2008), and associations between physical activity and cognitive health have been reported in older breast and colorectal cancer survivors (Fitzpatrick, Edgar, & Holcroft, 2012).

MODIFIABLE FACTORS AND INFLAMMATION

Several unavoidable factors increase the likelihood of activated inflammatory pathways in BCS during treatment, including cancer pathology, surgery, chemotherapy, and radiation (Cheung et al., 2013). After treatment ends, it is possible that other psychosocial or behavioral factors may increase the likelihood of ongoing inflammation as well as problems with cognitive function in BCS. Robust relationships have been reported between several modifiable factors and inflammatory markers in the general population, including aging adults. Systematic reviews were conducted on the relationships between the variables of interest (stress, social isolation, physical activity, and sleep quality) and both inflammation and cognitive function with a focus on what is

known in oncology populations. The details of each of these reviews including the search criteria and key words are described in the individual sections below.

Psychosocial Factors and Inflammation

Perceived Stress and Inflammation

It is widely accepted that stress has direct effects on several regulatory systems in the body including the HPA axis and sympathetic nervous system, both of which modulate immune processes such as inflammation (Yang et al., 2013). In the general population, chronic psychological stressors have measurable effects on inflammatory processes and inflammation is now recognized as a biomarker for stressors such as job stress, low socioeconomic status, caregiver stress, and loneliness (Nakata et al., 2012; Hänsel, Hong, Cámara, & von Känel, 2010; Miller et al., 2008). The most common and consistently detected inflammatory markers that are linked to psychological stressors are cytokines—specifically IL-6, TNF-α and IFN-gamma (Hansel et al., 2010).

In otherwise healthy adults, positive relationships between psychological stress, IL-6, and C-reactive protein (CRP) have been reported (Ranjit et al., 2007). Glei et al. (2013) reported that higher perceived stress was predictive of greater inflammatory dysregulation among women from the U.S but not men suggesting gender differences in immune responses to stress. In one study of older adults, inventories of stressful events in the last 24 hours were positively related to IL-6 (β =.05, t(109)=2.06, p =.04) and CRP levels (β = .9, t(129) = 2.14, p =.04) (Gouin, Glaser, Malarkey, Beversdolf, & Kiecolt-Glaser, 2012); but no significant relationships were reported between inventory of stressful events and TNF-α in another study (Luz et al., 2003). Similarly, in a longitudinal study of adults caring for spouses with Alzheimer's disease (N=118), the stress of longer time spent caregiving was associated with elevated CRP levels (p = 0.04) and caregivers showed greater TNF-α levels than controls (n=51; p = .048; von Kanel et al., 2012). In a

study of healthy young adults exposed to a laboratory stressor, significant increases in inflammatory markers— sTNF αRII and IL-6— were reported (Slavich, Way, Eisenberger, & Taylor, 2010); but, no relationship between IL-6 and acute laboratory stress was found in another study (Aschbacher et al., 2012).

In persons with MS, moderate positive relationships between perceived stress and IL-6 (r=.428, p<.01) and IL-10 (r=.441, p<.01) have been reported (Sorenson, Janusek, & Mathews, 2013). In persons with rheumatoid arthritis, higher chronic interpersonal stress was associated with greater stimulated IL-6 production (p<.05); however, chronic stress ratings were not related to plasma levels of IL-6 or CRP (p's > .05; Davis et al., 2008).

A literature review of primary research studies evaluating perceived stress and inflammation in breast cancer patients was conducted in Pubmed from 2005 to 2015. First, a search of these variables was conducted using the key words: perceived stress, psychological stress, inflammat*, proinflammat*, cytokines, IL-6, TNF-α, psychoneuroimmunology, and breast cancer. Studies that included data on relationships between perceived stress factors and inflammation in the identified populations were included. Animal and in vitro studies, studies evaluating risk for developing breast cancer, and pharmaceutical clinical trials were excluded. The search was expanded to all oncology populations for a more comprehensive understanding of the relationships among people who experience a cancer diagnosis (expanded key words: oncology, cancer). The findings of this review are reported in Table 2.2.

Seven studies were identified in the literature. Six of these studies included BCS during or after treatment. Four studies utilized prospective designs and two were quasi-experimental.

Table 2.2

Stress, Perceived Social Isolation, and Inflammation in Oncology Populations

First Author, Year	Objective	Design	Sample	Psychosocial Variable (s)	Inflammatory Variable(s)	Key Findings
			Stress			
Oncology						
Archer, 2012	To investigate whether childhood trauma, recent life events, and increased levels of inflammatory markers are risk factors for increased depressive symptoms following cancer diagnosis and treatment	Prospective T1: 6 weeks post-diagnosis T2: 12 weeks post-diagnosis T3: 24 weeks post-diagnosis	Newly diagnosed cancer patients (56 head and neck cancer, mean age 63 (13) and 34 colorectal cancer, mean age 70 (10.1))	Stressful life events in the last 6 months (Brief Life Events Questionnaire) Childhood Trauma (Childhood Trauma Questionnaire)	Cytokines (IL1ß, TNF- α, IL6, IFNg CRP)	Childhood trauma predicted higher levels of CRP levels at baseline and TNF- α levels at one week post-surgery in CRC patients (n=18, *B*(CI)=0.09 (0.01 to 0.17) *p*=0.033, n=18, *B*(CI)=0.03 (0.01 to 0.05) *p* =0.007 respectively) There was no evidence of a relationship between childhood trauma and increased inflammation in head and neck patients
Bower, 2007	To examine inflammatory responses to a stressor and their relationship to circulating glucocorticoids	Quasi-Experimental pre/post-test: participants exposed to laboratory stressor (Trier Social Stress Task)	BCSs stages 0-II (N=25; 10 fatigued [mean age 55], 15 non-fatigued [mean age 61.7])	Acute Stress (TSST: preparing and delivering an impromptu speech to a panel)	IL-1, TNF- α, IL-6 (ELISA) Glucocorticoids	From pre stress to post stress-significant effect of time for IL-1 β (F (1, 20)= 10.9, p= .004) and for IL-6 (F (1, 20)= 8.1, p= .01) and TNF- α (F (1, 20)= 3.9, p= .06) Non-fatigued survivors

Table 2.2 (continued)

						showed a significant increase in salivary cortisol concentrations following the test
Carlson, 2007	To investigate the ongoing effects of participation in a mindfulness-based stress reduction (MBSR) program on quality of life, symptoms of stress, mood and endocrine, immune parameters	Quasi-experimental repeated measures pre-intervention, post-intervention, 6 & 12 months later	Breast (n=49) and prostate survivors (n=10) stages 0-II	Responses to stressful situations (SOSI)	Interferon gamma (IFN-c?), TNF- α, IL-4, IL-10 (flow cytometry) Salivary cortisol (ELISA)	Significant relationships were reported between high perceived stress scores and TNF-α (r =0.39, p <0.05) and IL-4 (r=-0.37, p <0.05)
Cross-well, 2014	To examine the associations between childhood adversity and heightened inflammation in BCSs	Cross sectional	BCSs (Stages 0 to IIIA) completed primary cancer treatment 1 year earlier (n = 152)	Three types of childhood adversity-abuse, neglect, and a chaotic home environment (Risky Families questionnaire) Stress (PSS)	IL-6; IL-1β; TNF-α, CRP: (ELISA)	Combined measure of childhood adversity predicted elevations in plasma levels of IL-6 (β = 0.009, p = .027, η^2 = 0.027, after controlling for age, BMI, ethnicity, alcohol use, and cancer treatment (surgery, radiation, and/or chemotherapy)
Han, 2015	To examine if breast cancer patients with childhood	Prospective, longitudinal study T1: 1 week prior to radiation	Breast cancer patients (n=20), stage 0-IIIA	Exposure to childhood trauma (Childhood	mRNA; NF-kB DNA binding; sTNFR2; IL-1ra; IL-6; CRP (blood	PSS scores correlated with CRP (r= .81, p =0.015), IL-6 (r=.71, p<.05) at time 1; and with CRP (r= .81, p <0.05),

Table 2.2 (continued)

	trauma exhibit increased fatigue, depression, and stress in association with inflammation as a result of whole breast radiotherapy	T2: Week 6 of radiation treatment T3: 6 weeks after radiation		trauma questionnaire) Stress (PSS)	taken prior to radiation initiation)	IL-1ra (r=.78, p<.05) for those with childhood trauma but not in those without No significant correlations between symptoms and sTNFR2 or NF-kB DNA binding at baseline were found at any time in all subjects
Wenzel, 2012	To examine the effect of mother's vital status on psychological factors and stress-associated biomarkers among BRCA mutation carriers	Mixed methods: surveys and focus groups	Women with BRCA 1or 2 mutations, mixed histories of cancer occurrences (N=32)	Stress (PSS) Disease specific stress (IES)	Salivary cortisol and dehydroepian-drosterone (DHEA) levels	Among those whose mothers were deceased, there is a correlative trend between post-focus group stress, anxiety (r = 0.40, p = 0.13), and salivary cortisol (r = 0.44; p = 0.09)
Witek-Janusek, 2007	To evaluate women's psychological and immunological response to breast biopsy (stressful experience)	T1: enrollment T2: day of biopsy T3: 1 month after biopsy T4: 4 months after biopsy	Women with BC (n=22) Women without (n=29)	Stress (PSS) Mood (POMS)	IL-2, IL-6, IFN gamma, IL-4 (quantitative sandwich enzyme immunoassay)	IL-4, IL-6, and IL-10 production were increased before and after the procedure (stressful experience) compared to the control group (women without BC)
Social Isolation						
Oncology Population						
Jaremka, 2013	To examine whether loneliness is	Quasi-experimental measuring T1:	Breast-cancer survivors Stages 0 to IIIA, completed	Loneliness (UCLA-R)	IL-1β; TNF-α; IL-6 (electrchemi-	Loneliness unrelated to changes in stimulated TNF-α production from before to after stress, b =

Table 2.2 (continued)

	linked to stress-related pro-inflammatory cytokine production	before stress T2: 45 after stress and T3: 2 hr after stress	cancer treatment (N = 144) mean age 51.44 (9.17)		luminescence)	0.14, F (1, 129) = 2.33, p = .130 Lonelier participants exhibited greater synthesis of IL-6 and IL-1β than participants who were less lonely—IL-6: b = 0.53, F (1, 129) = 4.48, p = .036; IL-1β : b = 0.42, F (1, 131) = 7.21, p = .008.
Marucha, 2005	To examine how disruptions in social activities relate to TNF- α responses	Prospective: T1 at time of diagnosis T2 after surgery T3 12 months later	Newly diagnosed breast cancer patients stage I or II (N=44) Mean age 52.05 (10.18)	Family, social, and leisure activities (Katz Social Adjustment Scales) Partner satisfaction (Dyadic Adjustment Scale)	TNF-α (ELISA)	Decreases in social engagement explained significantly more variance in TNF-α levels at the 12 month follow up above and beyond baseline TNF-α levels and cancer stage alone (r^2 change=0.094, p<0.05) Decreases in both social engagement and partner satisfaction explained significantly more variance in TNF-α levels at the 12 month follow up above and beyond baseline TNF-α levels and cancer stage (r^2 change=0.172, p<0.05)
Muscatell, 2015	To investigate upstream neural processes that may link psychosocial stressors and inflammation	Cross sectional	Early-stage breast cancer who completed treatment (n=15) Age matched controls (n=15) Average age 55 years	Perceived social attachment/ Support (Social Provisions Scale)	CRP and IL-6 (blood)	Moderate negative correlation between social support/attachment and CRP levels (r = -.55, p = .03) in the survivor group Moderate relationship between social support with IL-6 levels

Table 2.2 (continued)

	in cancer patients and survivors					(r = -.37, p = .18) in the survivor group, but non-significant
Nausheem, 2010	To investigate the association of serum levels of proangio-genic cytokines indices of social support and loneliness	Cross sectional	Colorectal cancer patients (mean age 68.27 (10.12)	UCLA Loneliness Scale	VEGF, IL-6 (surgical biopsies of tumors of colon and rectum using streptavidin-biotin method)	Implicit loneliness predicted VEGF levels (OR 5.16, 95% CI 1.05–25.35, p=04) No significant correlation between explicit or implicit scores of loneliness (p = .27) and IL-6
Yang, 2014	To assess the associations between social network ties and multiple measures of inflammation	National Health and Nutrition Examination Survey III (1988–94)	Adults with cancer (n=1075)	Social network (SNI)	CRP; fibrinogen; albumin (plasma)	Those who were more socially isolated or had a SNI score of 3 or less exhibited increasingly elevated inflammation burdens adjusting for age and sex (b=.13-.24, p<.05) Higher SNI scores associated with lower values of logged CRP (p = .028) and fibrinogen (p = .038) and higher values of serum albumin

Note. **BCS**, BCSs; **fMRI**, functional magnetic resonance imaging
Bio Markers: **CRP**, c-reactive protein; **ELISA**, enzyme-linked immunosorbent assay, **HbA1c**, hemoglobin A1c; **IL**, interleukin; **IFN**, interferon; **IGF**-1, Insulin Growth Like Factor- 1; **NF**, nuclear factor; **sTNF-αRII**, soluble TNF-α Receptor II; **VEGF**, vascular endothelial growth factor
Self Report Scales: **PSS**, Perceived Stress Scale; **PANAS**, Positive an Negative Affect Scale; **POMS**, Profile of Moods Scale; **SOSI**, Symptoms of Stress Inventory; **SNI**, Social Network Index; **UCLA-R**, UCLA Loneliness Scale Revived; **TSST**, Trier Social Stress Test

Among these studies, relationships between perceived stress (Carlson et al., 2007; Wenzel et al., 2012; Witek-Janusek, Gabram, & Mathews, 2007), laboratory induced stress (Bower et al., 2007), history of childhood adversity (Archer, Hutchison, Dorudi, Stansfeld, & Korszun, 2012; Croswell, Bower, & Ganz, 2014; Han et al., 2015), and inflammatory factors were explored. For example, in a study of breast and prostate cancer patients, significant moderate relationships were reported between high perceived stress scores and TNF-α (r=.39, p<.05) and IL-4 (r-.37, p<.05; Carlson et al., 2007).

Summary

In summary, moderate positive relationships between perceived psychological stress and increases in circulating inflammatory biomarkers in the general population, (including older adults) and populations that have comorbidities are supported. In the oncology literature, most of the research on these relationships has been conducted in women either undergoing breast cancer treatment (Han et al., 2015; Wenzel et al., 2012;Witek-Janusek et al., 2007) or in survivorship (Bower et al., 2007; Carlson et al., 2007; Crosswell et al., 2014). There was heterogeneity in inflammatory markers used across these studies, however, TNF-α and IL-6 were utilized in five out of seven studies, and CRP in three of the seven. Of those studies that focused on BCS, only one study evaluated relationships between perceived stress and cytokines (Han et al., 2015). The authors reported strong positive relationships between perceived stress scores and CRP (r=.81, p=.015), IL-6 (r=.71, p<.05), and IL-Ra (r=.78, p<.05) in those BCS with a history childhood trauma but not in those without (N=20) (Han et al., 2015). The other two studies evaluated the inflammatory effects of an acute laboratory stressor (Bower et al., 2007) and how childhood adversities impacted plasma levels of cytokines (Crosswell et al., 2014). Due to publication bias, it is possible that studies that did not find relationships between these factors have not been published and therefore were not

reviewed in this proposal. This review highlights gaps in the literature regarding knowledge on the relationships between the construct of perceived stress and reliable, sensitive measures of inflammation such as IL-6 and TNF-α among BCS greater than one year after primary treatment ends.

Perceived Social Isolation and Inflammation

It is estimated that 15-30% of the adult population suffers from chronic perceived social isolation, or loneliness (Hawkley & Cacioppo, 2010). Loneliness has been described as perceived social isolation (Cacioppo & Hawkley, 2009; Hansel et al., 2010); however, this definition is not universally accepted (Boss, Kang, & Branson, 2015). In the general population, perceived social isolation has been associated with genetic under expression of anti-inflammatory glucocorticoid responses (Cacioppo & Hawkley, 2009). Positive links between both perceived and objective social isolation and impaired immunity have been reported in animal and human studies (Krügel, Fischer, Bauer, Sack, & Himmerich, 2014; Yang, Li, & Frenk, 2014). A recent review reported higher perceived social isolation was linked to increased pro-inflammatory cytokine response to stress and increased pro-inflammatory gene expression (Hawkley & Cacioppo, 2015). Furthermore, higher rates of loneliness are consistently associated with higher levels of IL-6 (Hansel et al., 2010).

Among healthy and older adults, evidence supports that greater social isolation is associated with higher inflammatory burden (Yang et al., 2013) and more perceived loneliness predicts greater levels of IL-6, TNF-α (Jaremka et al., 2013), interleukins, and MCP-1 (Hackett, Hamer, Endrighi, Brydon, & Steptoe, 2012) in regression analyses. Similarly, Cole et al. (2015) reported that greater loneliness predicted up–regulation of pro-inflammatory gene expression ($p<.05$) in community dwelling older adults. In older adults, significant, although weak, relationships between social isolation and CRP and

fibrinogen have been found (Shankar et al., 2011). Several studies have reported no relationships between loneliness and IL-6 (Shankar et al., 2011; Creswell et al., 2012), CRP (Creswell et al., 2012), and genetic markers of inflammation (Wang et al., 2013).

A literature review of primary research studies evaluating perceived social isolation and inflammation in breast cancer patients was conducted in Pubmed from 2005 to 2015. First, a search of these variables was conducted using the key words: perceived social isolation, loneliness, inflammat*, proinflammat*, cytokines, IL-6, TNF-α, psychoneuroimmunology, and breast cancer. Studies that included data on relationships between perceived social isolation and inflammation in the identified populations were included. Animal and in vitro studies, studies evaluating risk for developing breast cancer, and pharmaceutical clinical trials were excluded. The search was expanded to all oncology populations (key words: cancer and oncology) for a more comprehensive understanding of the relationships among people who experience a cancer diagnosis. The findings of this review are reported in Table 2.2.

Five studies were identified and three of the studies were conducted with breast cancer patients or survivors (Jaremka et al., Marucha, Crespin, Shelby, & Andersen, 2005; Muscatell, Eisenberger, Dutcher, Cole, & Bower, 2015). Evidence on relationships between loneliness and IL-6, (Jaremka et al., 2013; Nausheen et al., 2010), TNF- α was mixed (Jaremka et al., 2013; Marucha et al., 2005) in oncology populations. Moderate negative correlations between social support and CRP (Muscatell et al., 2015) and between loneliness and vascular endothelial growth factor (VEGF) levels (Nausheem et al., 2010) have been reported. Yang et al. (2014) reported that adult cancer survivors with greater social isolation had higher inflammatory burdens than adults without a history of cancer.

Summary

Taken together, few studies have evaluated perceived social isolation in BCS greater than one year after the end of primary treatment. The data from the reviewed studies is equivocal in regards to relationships between perceived social isolation and levels of inflammatory markers and there is heterogeneity in the type of biomarkers utilized. Further research is necessary to understand if there are relationships between these factors and if so, the quality of such relationships.

Behavioral Factors and Inflammation

Physical Activity and Inflammation

Physical activity and exercise have been found to help regulate pro-inflammatory pathways in the body (Nascimento et al., 2014). According to a systematic review, exercise induces a short-term inflammatory response and long-term anti-inflammatory effects (Kasapis & Thompson, 2005). In population-based studies, an inverse, independent, dose–response relationship has consistently been demonstrated between physical activity ("any bodily movement produced by skeletal muscles that results in energy expenditure" (Caspersen, Powell, & Christenson, 1985, p. 128) and markers of systemic inflammation—especially IL-6, TNF-α, and CRP (Beavers, et al. 2010). The relationship between CRP and physical activity is more consistently seen in men—"This sex discrepancy may be due to the fact that women have greater adiposity than men, a potential confounding factor in the association between physical activity and inflammation" (Beavers et al., 2010, p. 786).

In healthy adults, more physical activity, both subjective and objectively measured, has been associated with lower levels of inflammatory levels such as IL-6, CRP, IL-1b, and TNF-α (Adams et al., 2015; Fischer, Berntsen, Perstrup, Eskildsen, & Pedersen, 2007; Lee et al., 2012; Wu et al., 2014). Similarly, relationships between less

physical activity and higher levels of cytokines (IL-6, CRP, TNF- α) have been consistently reported cross-sectionally (Colbert et al., 2004; Taaffe, Harris, Ferrucci, Rowe, & Seeman, 2000). Lower levels of inflammatory cytokines (IL-6 and TNF-α) have been reported in controlled trials evaluating the effects of exercise in older adults (Nascimento et al., 2014; Starkweather, 2007). Additionally, it has been reported that those that are more physically fit have a lower inflammatory response to stress (Hammer & Steptoe, 2007). In a review of effects of exercise on inflammatory markers in persons with chronic inflammatory diseases, evidence supported that long-term endurance exercise can attenuate systemic inflammation in patients with chronic heart failure and type II diabetes (Ploeger, Takken, de Greef, Mathieu & Timmons, 2009). In the context of oncology, evidence supports the role of exercise in reducing inflammation (IL-6, TNF-α, MCP-1) especially in breast and colon cancer populations (Ballard-Barbash et al., 2012; Murphy, Enos & Velazquez, 2015).

A literature review of primary research studies evaluating physical activity and inflammation in oncology populations was performed in PubMed from 2005 to 2015. First, a search of these variables was conducted using the key words: physical activity, physical inactivity, exercise, inflammat*, proinflammat*, cytokines, IL-6, TNF-α, psychoneuroimmunology, and breast cancer. Studies that included data on relationships between physical activity or exercise and inflammation in the identified populations were included. Animal and in vitro studies, studies evaluating risk for developing breast cancer, and pharmaceutical clinical trials were excluded. The search was expanded to all oncology populations (key words: cancer and oncology) for a more comprehensive understanding of the relationships among people who experience a cancer diagnosis and the findings reported in Table 2.3.

Table 2.3

Physical Activity, Sleep Quality and Inflammation

First Author, Year	Objective	Design	Sample	Behavioral Variable	Inflammatory Variable	Key Findings
Physical Activity						
Oncology Populations						
Jones, 2013	To examine changes in plasma concentrations of the pro-inflammatory markers IL-6, CRP, and TNF-α in an exercise group compared to usual care	RCT of exercise in post-menopausal BCS Intervention:1 50 minutes of moderate intensity aerobic exercise for 5 weeks	BCS stages 0-IIIa (N=65) Mean age 56	PA (PA Questionnaire; 7 day activity log; 7 day pedometer log)	CRP; IL-6; TNF-α (serum, ELISA)	No significant effect of exercise on changes in inflammatory marker concentrations between women randomized to exercise versus usual care IL-6 and CRP were inversely correlated with pedometer steps per day (r =0.42, r =0.44; $p < 0.001$), TNF-α was not associated with either measure of baseline physical activity
Pakiz, 2011	To explore the effect of physical activity on inflammatory markers at the end of a 16 week intervention	RCT of cognitive behavioral therapy to reduce weight and increase physical	Obese BCS (intervention n=44; control n=24) Stages I-IIIA Mean age 56 (9)	PA (7-day physical activity recall)	TNF-α; IL-6; IL-8; VEGF (serum, ELISA)	Increased physical activity from baseline to 16 weeks was associated with favorable changes in IL-6 (r=−0.35, p<.05) and VEGF (r=−0.46, p <0.01) in the control group

Table 2.3 (continued)

		activity, weekly for 4 months, and follow-up monthly sessions through 12 months				Intervention group controlling for change in weight and change in heart rate/min after the stepping test, increased level of PA was associated with favorable changes in IL-6 levels (R^2=0.18; p<0.03)
Rogers, 2013	To examine mediators of fatigue response to an exercise intervention for BCS	Pilot RCT 4x/week for 3 months of exercise (combined aerobic and strength total weekly goal of 160 aerobic minutes, 26 total strength training sessions)	Postmeno-pausal BCS (n = 46; stages 0-II) after primary treatment	Cardiorespiratory fitness (sub-maximal treadmill test) Physical activity (accelerometer)	IL-6, IL-8, IL-10, and TNF-α (serum)	Positive effect size of physical activity on fatigue was significantly mediated by IL-6 (82%), IL-10 (94%), IL-6/IL-10 (49%), and TNF- α /IL-10 (78%)
Sleep Quality						
Oncology Populations						
Alfaro, 2014	To replicate the associations found in our previous study of patients and family caregivers between interleukin 6 (IL6) and nuclear factor	Prospective (Initial questionnaire completed prior to surgery and then monthly times 6)	Patients with BC (n=398), stages I-IV, mean age approximately 55(11) years	Sleep Disturbance (General Sleep Disturbance Scale)	Single nucleotide polymorphisms (SNP) for interferon gamma (IFNG), IFNG receptor 1 (IFNGR1), IL1R1, IL2, IL8,	In the analysis for IL13 rs1800925 carrying one or two doses of a rare T allele was associated with a 2.21-fold increase in the odds of belonging to the high sustained sleep disturbance class (p < .005)

Table 2.3 (continued)

	kappa beta 2 (NFKB2) and sleep disturbance				IL17A, NFKB1, NFKB2, and TNF-α (peripheral blood)	In the analysis for NFKB2 rs1056890 carrying one or two doses of a rare T allele was associated with a 47% decrease in the odds of belonging to the high sustained sleep disturbance class (p= .028).
Bower, 2011	To evaluate if fatigue, depression, and sleep disturbance share a common inflammatory processes	Cross sectional	BC survivors who recently finished treatment (n=103), mean age 51.2	Sleep quality (PSQI)	sTNF-RII, IL-1ra, and CRP (plasma ELISA)	Sleep problems were correlated with fatigue but not with inflammatory markers (all *p's* for PSQI >.80).
Bower, 2013	To test the hypothesis that expression-regulating polymorphisms in pro-inflammatory cytokine genes would predict post-treatment fatigue in BCS	Cross sectional Within 3 months of the end of primary treatment	BCS early-stage breast cancer (n =171), mean age 51	Sleep disturbance (PSQI)	(SNPs) in the promoter regions of three cytokine genes: ILB -511 C>T (rs16944), IL6-174 G>C (rs1800795), and TNF -308 G>A (rs1800629) (Genomic DNA extracted from peripheral-blood leukocytes)	Neither the genetic risk index nor any of the individual SNPs were significantly associated with subjective sleep quality
Clevenger, 2012	To examine relationships between sleep	Prospective observational study	Ovarian cancer patients prior to	Sleep quality: PSQI	IL-6 (ELISA)	Significant (p< .05) relationship between sleep disturbance and IL-6 at T1

Table 2.3 (continued)

	disturbance, fatigue, and plasma IL-6 in women with ovarian cancer prior to surgery	T1: before surgery T2: 1 year after end of adjuvant treatment	surgery (N=136) Disease free ovarian cancer survivors (n= 63)			and T2 (β=0.21, β=0.23) controlling for covariates Changes in sleep over time were significantly associated with percent change in IL-6 from T1 to T2 (β=.27, p < .01)— 10% decrease in IL-6 results in 0.13 point improvement in the global sleep change score
Sprod, 2010	To compare the influence of a home-based exercise intervention with standard care/control on sleep quality and mediators of sleep	Randomized, controlled phase 2 pilot study	Breast and prostate cancer patients receiving radiation (N=38),	Sleep quality: PSQI	IL-6, TNF-α, sTNF-R (ELISA)	Significant relationships were reported between TNF-α and sleep quality (r=0.33, p<.05) and sleep latency (r=.36, p<.05) Significant relationship between sleep duration and IL-6 (r=-0.49) in the intervention group sTNF-R was negatively associated with subjective sleep quality (r = − 0.36; p = 0.026, *CI*= − 0.610, − 0.046); sleep disturbances (r = − 0.42; p = 0.009; *CI* = − 0.651, − 0.115); and the use of sleep medications (r = − 0.33; p = 0.045; *CI* =− 0.586, − 0.008). IL-6 was positively associated with sleep duration

Table 2.3 (continued)

					(r = 0.35; p = 0.031; *CI* = 0.035, 0.603) and sleep efficiency (r = 0.39*; p* = 0.015; *CI* = 0.081, 0.613). Better sleep quality related to lower TNF- α; and higher concentrations of sTNFR overall and better sleep quality related to lower il-6 in intervention group

*Note***. PA**, Physical Activity
Bio Markers: **ELISA**, enzyme-linked immunosorbent assay, **HbA1c**, hemoglobin A1c; **IL**, interleukin; **IFN**, interferon; **IGF-1**, Insulin Growth Like Factor- 1; **CRP**, c-reactive protein; **sTNF-αRII**, soluble TNF-α Receptor II; **VEGF**, vascular endothelial growth factor

Self Report Scales: **RAPA** (Rapid Assessment of Physical Activity) **PANAS** (Positive an Negative Affect Scale); **POMS** (Profile of Moods Scale); **PSS** (Perceived Stress Scale); **SOSI** (Symptoms of Stress Inventory); **SNI** (Social Network Index); **UCLA-R** (UCLA Loneliness Scale Revived); **TSST** (Trier Social Stress Test); **PSQI** (Pittsburgh Sleep Quality Index)

Three randomized control trials were found evaluating the effects of physical activity or weight loss interventions on inflammatory markers in BCS. The findings on the effects of physical activity on IL-6, TNF- α were mixed. Jones et al. (2013) reported no significant effect of a RCT exercise intervention of 150 min of aerobic exercise for five weeks. Pakitz et al. (2012) reported that after controlling for weight loss and age, the intervention group's increases in physical activity explained 18% of the variance in favorable IL-6 changes ($p<.03$) after completing a year of a cognitive behavioral intervention. Additionally, moderate inverse relationships between increased physical activity and lower levels of IL-6, CRP and VEGF were found (Jones et al., 2013; Pakitz et al., 2011), and Rogers et al. (2013) reported that IL-6, IL-10, and TNF-α significantly mediated the effects of physical activity on self reported fatigue in BCS who underwent a combined aerobic and strength training exercise intervention over 12 weeks.

Summary

These studies highlight evidence supporting moderate, negative relationships between physical activity and inflammatory cytokines, especially IL-6, CRP, and TNF-α. This review provides preliminary evidence to support that inflammation may mediate the effect of physical activity on the health outcome fatigue; however, more research is necessary to understand how inflammation may mediate the effects of physical activity on other health outcomes, particularly cognitive function in BCS.

Sleep Quality and Inflammation

It is hypothesized that poor sleep quality (e.g. sleep disturbance and sleep restriction) may drive inflammation and subsequent cancer-related symptoms, including cognitive dysfunction (Miller, 2008; Irwin, 2013; Irwin, 2015). It is widely accepted that there are reciprocal relationships between sleep and immune responses—quality of sleep can impact the immune system and immune processes can impact sleep (Del Gallo, Opp

& Imeri, 2014). Clevenger et al. (2012) explain the bidirectional relationship between inflammation and sleep saying, "Inflammatory processes appear to be able to induce sleep disturbances via alterations in sleep architecture; conversely, sleep disturbances have been shown to induce inflammatory cytokines" (p. 7). Sleep loss is considered a risk factor for inflammatory diseases such as heart disease, Alzheimer's disease, and cancer (Hurtado-Alvarado et al., 2013). In a population-based study of women and men (N=4,642), a significant relationship between less sleep and higher levels of IL-6 (p<.05) was reported in women (Miller et al., 2009). Evidence supports significant negative relationships between poor sleep quality, fewer hours spent sleeping, and worse sleep efficiency and higher levels of IL-6 (Heffner et al., 2012; Kanel et al., 2006; Miller et al., 2009) in the general and elderly populations.

A literature review of primary research on sleep quality and inflammation in oncology populations was performed in PubMed from 2005 to 2015. First, a search of these variables was conducted using the key words: sleep, sleep initiation and maintenance disorders, insomnia, inflammat*, proinflammat*, cytokines, IL-6, TNF-α, psychoneuroimmunology, and breast cancer. Studies that included data on relationships between sleep quality or insomnia and inflammation in the identified populations were included. Animal and in vitro studies, studies evaluating risk for developing breast cancer, and pharmaceutical clinical trials were excluded. The search was expanded to all oncology populations (key words: cancer and oncology) for a more comprehensive understanding of the relationships among people who experience a cancer diagnosis and the findings reported in in Table 2.3.

Five studies were identified and all samples included breast cancer patients or survivors. One study also included ovarian cancer survivors (Clevenger, 2012) and another included prostate cancer patients (Sprod, 2010). The majority of these studies

utilized the Pittsburgh Sleep Quality Index to evaluate sleep quality and there was heterogeneity in terms of inflammatory markers measured. Two studies looked at genetic markers— multiple SNPs associated with pro-inflammatory genes (Alfaro et al., 2014; Bower, 2013), and three evaluated peripheral circulating cytokines— sTNF-RII, IL-1ra, CRP, IL-6, and TNF-α (Bower, 2011; Clevenger, 2012; Sprod, 2010). In the studies evaluating peripheral cytokines a moderate positive relationship between sleep quality and TNF-α (r=0.33) (higher scores on PSQI indicate worse sleep quality) and a moderate negative relationship between sleep duration and sTNF-R (r's=-0.33 to -.42) (Sprod, 2010) were reported. Additionally, sleep disturbance predicted changes in IL-6 (Clevenger, 2012); however, one of the studies found no significant relationships between sleep and sTNF-RII, IL-1ra, and CRP (p's >.80; Bower, 2011). The results of the studies evaluating genetic pro-inflammatory factors in relation to sleep disturbance were mixed (Alfaro et al., 2014; Bower, 2013).

Summary

In summary, these studies were mainly conducted on cancer patients undergoing treatment, and may not reflect accurate data for survivors who have completed active treatment. These studies suggest that moderate relationships may exist between sleep quality and inflammatory markers, but further research is necessary to understand the direction and quality of these relationships in BCS six months to 10 years into survivorship.

MODFIABLE FACTORS AND COGNITIVE FUNCTION

Evidence also supports associations between the aforementioned modifiable factors and cognitive function in the general adult population but these relationships have not been specifically evaluated in BCS.

Psychosocial Factors and Cognitive Function

Perceived Stress and Cognitive Function

The relationships between psychological stress and cognitive function are well documented (Marin et al., 2011; Leng et al., 2013). For example, a population-based study of adults 65 years or older (N=6,207) reported independent relationships between perceived stress and both cognitive scores and cognitive decline on a task of perceptual speed (p<0.001; Aggarwal et al., 2014). In recent years, theories have been proposed to suggest that the etiology of CRCI might be explained by psychosocial factors such as allostatic load (Andreaotti et al., 2015) and overloaded self-regulatory systems (Arndt, Reid-Arndt, Das, Cameron, Ahles, & Schagen, 2014; Cacioppo & Hawkley, 2009). It has been suggested that exposure to prolonged psychological stressors (including cancer and cancer treatment) can overload a persons' neurological allostasis and result in neural biological changes and subsequent cognitive changes (Andreaotti et al., 2015).

A literature review of primary research on perceived stress and cognitive function in oncology populations was performed in PubMed from 2005 to 2015. First, a search of these variables was conducted using the key words: perceived stress, psychological stress, cognitive function, cognitive dysfunction, cogniti*, cognitive decline, and breast cancer. Studies that included data on relationships between perceived stress cognitive function in the identified populations were included. Animal and in vitro studies, studies evaluating risk for developing breast cancer, and pharmaceutical clinical trials were excluded and the findings reported in in Table 2.4.

Significant moderate relationships were reported between perceived stress and both perceived cognitive function (Li, Yu, Long, Li, & Cao, 2014; Myers, Wick, & Klemp, 2015; Ottati & Feuerstein, 2013) and cognitive performance—general cognitive decline (Mehlsen, Pedersen, Jensen, & Zachariae, 2009), immediate memory(r=.43),

Table 2.4.

Stress, Perceived Social Isolation, and Cognitive Function

First Author, Year	Objective	Design	Sample	Psychosocial Variable (s)	Cognitive Variable	Key Findings
Stress						
Oncology Populations						
Ottati, 2013	To develop a brief self report measure of work-related stress and cognitive limitations	Secondary analysis	BCS, stage I-III, from 2 studies (n=228)	Job stress (1 item: "How often do you experience job stress at work (never, seldom, sometimes, often)?")	Global cognitive function (FACT-COG) Perceived Attention, Concentration, memory, visual processing, language, executive functioning (CSC-W59)	Job related stress significantly correlated with FACT-COG (r=.43, p<.001) and the CSC-W59 (r=.35, r<.001)
Li, 2014	To investigate how chemo and psychological factors are related to perceived cognitive impairment	Cross sectional observational	Breast cancer patients, Stage 0-IV (n=202) Mean age 45.2 (8.0)	PTSD Symptoms (PTSD Symptom Inventory)	Perceived Cognitive Impairment (Chinese version of FACT-Cog Version 3)	Perceived cognitive impairment was negatively related to avoidance (r=-.45, p<.001) and hyper-arousal (r=-.57, p<.001)
Mehlsen, 2009	To examine if cancer patients receiving chemo differ in cognitive changes from cardiac patients	Prospective observational T1 (0-7 days before chemo) T2 (4-6 weeks after last cycle	Breast cancer patients receiving chemo (n=34)	Stress (PSS)	Working Memory (WAIS-III, Digit span Forward and Backward) Response Inhibition (Stroop Test)	Baseline stress was the only significant predictor of general cognitive decline in the breast cancer patients (Odds ratio: 1.3, p<. 01)

Table 2.4 (continued)

	and healthy controls	of chemo)	Age 48.6 (8.0) Cardiac patients (n=14) Healthy controls (n=17)		Processing speed (WAIS-III) Executive functioning (Shifting Attention) Verbal memory (RAVLT WAIS-III immediate and delayed) Visual memory (RCFT immediate and delayed) Visuospatial ability (RCFT) Verbal fluency (Word Fluency-animals, "f", "n")	No differences with respect to changes in cognitive performance over time between the three groups
Phillips, 2010	To compare cognitive effects of adjuvant tamoxifen and letrozole in postmenopausal early stage breast cancer patient	Sub-study (Cross sectional, 5 years after endocrine treatment) of a double blind RCT	Breast Cancer Patients (n=120) 63.7 (7) years old	Psychological Distress (GHQ-12)	Psychomotor function, visual attention, working memory, visual learning, verbal learning (set of computerized cognitive tests)	No correlation was observed between cognitive composite score and perceived psychological distress Those taking letrozole had better overall cognitive function than those taking tamoxifen (mean difference in composite z-scores. 0.28, p= 0.04, 95% CI: 0.02, 0.54, d= . 0.40)
Boykoff, 2009	To examine the psychosocial	Ethnographic Content	BCSs (n=74)	Psychosocial Stress	Perceived Memory	Women in the sample identified that they had

Table 2.4 (continued)

	effects of chemobrain	Analysis (part of exploratory pilot study) focus groups	40-59 years (65%)			more memory dysfunction in stressful situations such as job interviews
Munir, 2011	To examine the need for interventions related to perceived cognitive problems from the perspectives of cancer patients and healthcare staff	Part of a mixed methods study (combined qualitative and quantitative content analysis), interviewed 4 months after completing chemo Semi structured interviews	BCSs, Stage I-III (n=31) Oncology Health Providers (n=5) 47 (6) years	Psycho-social Distress	Perceived global cognitive problems	Participants perceived that an intervention targeted at coping with emotional stress associated with cognitive problems would be "quite a bit useful to "very useful"
Myers, 2015	To explore potential factors associated with perceived cognitive impairments in BCSs compare to controls	Cross sectional	BCSs (n=317) Mean ages range 53.1-62.3 for 5 groups of BCS Stage I-IV (majority stage II) Type of chemo unspecified Healthy controls (n=	Distress (MD Anderson Symptom Inventory)	Perceived Cognitive Function (AFI; FACT-Cog)	Perceived cognitive impairments were associated with distress (r = -.40, p<.0001) AFI were associated with distress (r = -.40, p<.0001) Significant group effect was seen for PCI (F (6, 355)=7.01, p<0.0001)—controls reported less PCI than other groups

Table 2.4 (continued)

			46)			
Reid-Arndt, 2011	To evaluate the relationship between stress and cognitive impairments and the potential role of coping style as a mediator	Cross sectional	Breast cancer patients after surgery (n=36)	Stress (IES-R) Coping (MAC; Brief COPE)	Cognitive Performance (Rey Trials; COWAT; WAIS Digit Span)	Perceived stress was significantly related to scores on measures of immediate memory (r=-.43, p<.01), delayed memory (r=-.43, p <.01), verbal fluency (r=-.37 p<.05), and attention (r=-.42, p<.01) Helplessness mediates the relationship between self reported stress and cognitive functioning (p<.01)
Perceived Social Isolation						
Oncology Populations						
Cheung, 2012	To gather descriptions from multiethnic Asian breast cancer patients on their experiences and impact of chemo associated cognitive changes	Qualitative Descriptive (eight focus groups)	Breast cancer patients receiving chemo (N=43) Mean age 52 Stages I-IV (77% stages II or III)	Social Support	Perceived cognitive changes	26% of participants attributed cognitive changes to lack of social support
Deckx, 2015	To evaluate social and emotional loneliness in older	Prospective T1: baseline T2: 1 year after	Older breast and Colorectal	Loneliness (Loneliness scale of De	Cognitive Functioning (EORTC QLQ-C30)	Older survivors who were impaired on cognitive functioning

Table 2.4 (continued)

cancer patients compared to younger cancer patients and older people without cancer	baseline	Survivors (n=125) Younger breast and Colorectal Survivors (n=196) Older Control group (n=215)	Jong-Gierveld)	were at increased risk of becoming lonely (OR 2.84 95% CI 1.5-5.37) Older survivors who became cognitively impaired were at increased risk of becoming lonely (OR 3.00 95% CI 1.65-5.44) Older survivors who were persistently cognitively impaired were at increased risk of becoming lonely (OR 5.77 95% CI 3.08-10.81) At baseline, older cancer patients were less lonely compared with older people without cancer At time 2 emotional loneliness had significantly increased for older cancer patients (26–42%, $p<0.001$) Emotional loneliness increased for younger cancer patients (25–34%,

Table 2.4 (continued)

						p = 0.02) but not for those without cancer
Jaremka, 2014	To examine the relationship between loneliness and cognitive function in BCSs using 3 samples (* only Study 1 reported here, studies 2a and 2b included healthy controls with breast cancer participants)	Study 1 part of a clinical trial	BCSs (n=200) Age 51.48 (9.24) Stage 0-IIIA 61% received chemo	Loneliness (UCLA-R)	Memory Concentration (3 item cognitive problems scale)	Lonelier BCSs reported more cognitive difficulty than less lonely survivors (b= .03, t(177)= 3.13, p=.002) across different treatment types
Mehlsen, 2009	To examine if cancer patients receiving chemo differ in cognitive changes during treatment from cardiac patients and healthy controls	Prospective observational T1 (0-7 days before chemo) T2 (4-6 weeks after last cycle of chemo	Breast cancer patients receiving chemo (n=34) Age 48.6 (8.0) Stage unspecified All had CEF chemo Cardiac patients (n=14) Healthy controls	Social support (Social Support Questionnaire of Transactions)	WAIS-III, Digit span Forward and Backward; Stroop Test; Shifting Attention; RAVT; WMS-III immediate and delayed; RCFT immediate and delayed; Word Fluency-animals, “f”, “n”	Social support was not a significant predictor of cognitive decline

Table 2.4 (continued)

(n=17)

Note. Self Report Measures**: AFI**, Attentional Function Index; **AGECAT**, Automated Geriatric Examination for Computer Assisted Taxonomy **BAI**, Beck Anxiety Inventory; **CES-D**, Center for Epidemiologic Studies Depression Scale Revised; **CSC-W59**, Cognitive Symptom Checklist Work-59; **EORTC-CFS**, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 version 3.0; **FACT-COG**, Functional Assessment of Cancer Treatment Cognition; **FEDA**, **GSDS**, General Sleep Disturbance Scale; **GHQ-12**, General Health Questionnaire- 12; **GLT-EQ**, Godin Leisure Time- Exercise Questionnaire; **HADS**, Hospital Anxiety Depression Scale; **IES-R**, Impact of Event Scale—Revised; **LSNS-6**, Lubben Social Network Scale–6; **MMQ**, Memory Questionnaire Ability Scale; **MAC**, Mental Adjustment to Cancer; **MASQ**, Multiple Ability Self-Report Questionnaire; **PANAS**, Positive and Negative Affect Schedule; **PAOFI**, Patient's Complaints of Own Functioning Inventory; **PSS**, Perceived Stress Scale; **PSQI**, Pittsburgh Sleep Quality Index; **PTSD**, Post Traumatic Stress Disorder; **UCLA-R,** UCLA Loneliness Scale Revised

NP Tests: **COWAT**; Controlled Oral Word Association Test; **HVLT-R**, Hopkins Verbal Learning Test Revised; **RAVLT**, Rey Auditory Verbal Learning Test; **RCFT**; Rey Complex Figure Test; **TMT A/B**, Trail Making Test A or B; **WAIS-III***,* Wechsler Adult Intelligence Scale 3rd edition; **WCST**, Wisconsin Card Sorting Test*;* **WMS-III**, Wechsler Memory Scale III

delayed memory (r=-.43), verbal fluency (r=-.37), and attention (r=-.42 p's<.05; Reid-Arndt, 2011). Perceived stress was identified as a predictor of cognitive decline in BCS (Mehlsen et al., 2009). In three qualitative studies, BCS identified that their stress negatively impacts their cognitive abilities (Boykoff et al., 2009; Munir et al., 2011). Only one study of BCS failed to find significant relationship between perceived stress and cognitive performance (Philips et al., 2010).

Summary

Taken together, there is strong evidence to support the relationship between perceived stress and perceived cognitive function in BCS and breast cancer patients. Two of the studies evaluated these concepts in BCS more than one year after treatment (Myers, 2015; Phillips, 2010). There was heterogeneity in cognitive tasks utilized to evaluate cognitive performance across the reviewed studies, making it is difficult to aggregate all the data; therefore, more data is needed to better understand the relationship between perceived stress and cognitive performance in BCS more than one year after primary treatment ends.

Perceived Social Isolation and Cognitive Function

Quality and frequency of social interactions are also associated with cognitive functioning (Kremen, Lachman, Pruessner, Sliwinski, & Wilson, 2012). Perceived social isolation, which is tied to the quality (rather than the quantity) of social interactions, has been shown to predict various health outcomes above and beyond objective measures of social isolation. Research indicates that perceived social isolation, or loneliness, is a risk factor for poorer cognitive performance and faster cognitive decline (Cacioppo & Hawkley, 2009). For instance, in an experimental manipulation of loneliness, imagined future isolation predicted cognitive changes even though objective isolation was not manipulated (Cacioppo et al., 2006 cited in Cacioppo & Hawkley, 2009). Furthermore,

higher perceived social isolation has been linked to impaired executive control and regulation (Hawkley & Capitanio, 2015), global cognition, processing speed, immediate and delayed recall (Boss et al., 2015).

Perceived social isolation is an established predictor of cognitive decline in older adults and is known to impair executive function in healthy adults (Cacioppo & Hawkley, 2009). In older adults, evidence suggests that more loneliness (Holwerda et al., 2012; O'Launaigh et al., 2014; Shankar, Hamer, McMunn, & Steptoe, 2013) or social isolation (DiNapoli, Wu, B Gow, Corley, Starr, & Deary & Scogin, 2014) is related to worse cognitive function. More social support (Gow et al., 2013) and better social integration (Ertel, Glymour, M., & Berkman, 2008) are related to better cognitive functioning. In one study of older adults social isolation was not related to cognitive functioning (Holwerda et al., 2012). Moreover, psychosocial isolation as a result of feeling overly stressed directly impairs neurocognitive function (Shankar et al., 2011) and perceived social isolation has been linked to poor sleep quality and shorter sleep duration (Hawkley & Capitanio, 2015).

A literature review of primary research on perceived social isolation and inflammation in oncology populations was performed in PubMed from 2005 to 2015. First, a search of these variables was conducted using the key words: perceived social isolation, loneliness, cognitive function, cognitive dysfunction, cogniti*, cognitive decline, and breast cancer. Studies that included data on relationships between perceived stress and cognitive function in the identified populations were included. Animal and in vitro studies, studies evaluating risk for developing breast cancer, and pharmaceutical clinical trials were excluded and the findings are reported in in Table 2.4.

Summary

In breast cancer patients and survivors loneliness was linked to worse cognitive functioning and cognitive decline (Cheung, et al. 2012; Jaremka et al., 2014; Mehlsen et al., 2009). Interestingly, one study found that cognitive decline was a significant risk factor for developing loneliness for older cancer survivors, suggesting that there may be a bidirectional relationship between loneliness and cognitive functioning in older survivors of various cancer types (Deckx et al., 2015). More research is needed to better understand the quality and strength of the relationship between perceived social isolation, or loneliness, and cognitive functioning in BCS, especially greater than one year after primary treatment.

Behavioral Factors and Cognitive Function

Physical Activity and Cognitive Function

Vascular health has been linked to cognitive status in the aging literature. It is proposed that one of the key mechanisms of improved cognitive abilities is through exercise, which preserves vessel elasticity (Gauthier et al., 2015). Several meta-analyses support that physical activity is associated with improvements in cognitive performance in older adults (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008; Uffelen et al., 2008; Smith et al., 2010). It is well documented that higher physical activity levels are associated with better cognitive function in older adults (Bherer et al., 2013; Bherer, 2015; Yaffe, Falvey, & Hoang, 2014) and that physical activity is a significant mediator of cognitive decline in healthy older adults (Bherer et al., 2013). Additionally, there is an inverse relationship between amount of physical exercise and risk for dementia along with cognitive decline in aging adults (Palliard, 2015). In older adult populations, significant positive effects of exercise interventions on cognitive performance and perceived cognitive function were reported in three RCT's (Nascimento et al., 2014;

Nishiguchi et al., 2015; Rahe et al., 2015) and a bidirectional relationship between physical activity and memory was also reported (Krall, Carlson, Fried, & Xue, 2014).

A literature review of primary research on physical activity and cognitive function in breast cancer populations was performed in PubMed from 2005 to 2015. Ten studies were identified, therefore, the population parameter was not expanded to all oncology populations. First, a search of these variables was conducted using the key words: physical activity, physical inactivity, exercise, cognitive function, cognitive dysfunction, cogniti*, cognitive decline, and breast cancer. Studies that included data on relationships between physical activity and cognitive function in the identified populations were included. Animal and in vitro studies, studies evaluating risk for developing breast cancer, and pharmaceutical clinical trials were excluded and the findings are reported in in Table 2.5.

Summary

Physical activity has been evaluated in oncology populations and in BCS more physical activity is related to visual memory (Crowgey et al., 2014), better frontal lobe controlled cognitive functions (Miki, Kataoka, & Okamura, 2014), and has been found to mediate the negative effects of high BMI on perceived cognitive functioning (Myers et al., 2015). Lower cardiorespiratory fitness is significantly related to lower hippocampal volume (Chaddock-Heyman et al., 2015). Having regularly participated in exercise in the previous three months was significantly related to better attention function in a large group of young BCS (Pradhan, Stump, Monahan, & Champion, 2014). Being in the highest and middle tertiles of physical activity were associated with better executive functioning and attention in BCS (Hartman et al., 2015). Not meeting CDC guidelines for physical activity was affiliated with an increased likelihood to have cognitive efficiency problems in adult survivors of childhood cancers (Krull et al., 2011). In two qualitative

Table 2.5

Physical Activity, Sleep Quality and Cognitive Function

First Author, Year	Objective	Design	Sample	Behavioral Variable (s)	Cognitive Variable (s)	Key Findings
Physical Activity						
Breast Cancer Populations						
Chaddock-Heyman, 2015	To explore whether cardiorespiratory fitness may hold promise for lessening declines in brain and cognitive health of a sample of BCS within 3 years of completion of primary cancer treatment	Cross sectional	BCS within 3 years of completion of primary cancer treatment (n=29) Non- cancer female controls (n=27)	Cardiorespira-tory fitness (submaximal graded exercise treadmill test)	Hippocampal volume (MRI) Cognitive Performance (spatial reconstruction task)	Cardiorespiratory fitness and total hippocampal volume were positively correlated in the cancer survivor (r = 0.37, p = 0.04) but not controls More fit BCS had comparable hippocampal volumes to non-cancer control participants (Cohen's d = 0.13; p > 0.3) Less fit BCS showed significantly smaller hippocampal volumes compared to both lower fit and higher fit control participants (Cohen's d = 0.87, p < 0.05) Higher fit and lower fit cancer survivors did not differ from higher fit and lower fit control participants in terms of spatial reconstruction
Cheung, 2012	To gather descriptions from multiethnic Asian breast cancer patients on their experiences ad impact of chemo	Qualitative Descriptive 8 focus groups	Breast cancer patients receiving chemo (N=43) Mean age 52 Stages I-IV	Physical Activity	Perceived cognitive changes	Many women (56%) attributed cognitive changes to lack of mental and physical activity

Table 2.5 (continued)

	associated cognitive changes					
Crowgey, 2014	To examine the relationship between self reported exercise, cardiorespiratory fitness, and cognitive function	Cross-sectional	ER+, HER-, Breast cancer patients (n=37), Stage IA-treated with chemo	Exercise (GLT-EQ); Cardiorespiratory Fitness (VO_{2peak})	Cognitive Performance (Finger Tapping and Symbol Digit Coding, Stroop Test; Symbol Digit, Four Part Continuous Performance Test	Significant positive relationship between exercise behavior and visual memory (r=.47, p=.004) Trend towards significance for the relationship between memory composite and exercise (r=.31, p=.067) All other relationship were generally weak and non-significant
Galantino, 2012	To identify the impact of yoga on measures of cognition, functional outcomes, and quality of life for BCS	Mixed Methods—Prospective Questionnaires and Focus Groups T1: Baseline T2: 6 weeks during chemo T3: 12 weeks during chemo, T4: 1 month after treatment conclusion T5: 3 months after treatment conclusion	Stage II breast cancer (N=4), age 44-65 years	Balance and flexibility (Functional Reach test (balance) and Sit and Reach test (flexibility)	Perceive Cognitive Function (Perceived Cognition Questionnaire) Cognitive Performance (CogState)	After 12 weeks of a yoga intervention (2x per week)— There was a reduction in errors and improvement in speed in at least half of the women in our case series
Hartman, 2015	To assess the relationship of obesity, physical activity, and sleep, with cognitive functioning among BCS	Cross Sectional	BCS, stages 1-3 (N= 136) Mean age 62.6 years (6.6), 65% received chemo	Physical Activity (global physical activity questionnaire (GPAQ)	Cognitive performance on memory, executive function, visual–spatial processing, verbal function,	Highest tertile of physical activity significantly related to better performance on the executive functioning domain (β = 5.13, SE = 2.42, p = 0.036) and attention domain (β = 4.26, SE = 2.07, p = 0.042) Middle tertile of physical activity significantly related to better

Table 2.5 (continued)

					attention, information processing speed, and motor skills	performance on the visual–spatial domain (β = 9.00, SE = 3.09, p = 0.004).
Krull, 2011	To examine neurocognitive and emotional functioning in relation to health behaviors in adult survivors of childhood cancers	Prospective Cohort from the Childhood Cancer Survivor Study	Adult Survivors of childhood cancers (n=6440)	Physical activity (weekly minutes of moderate and vigorous activity dichotomized into meeting CDC guidelines or not)	Cognitive Performance (4 subsets Task Efficiency, Emotional Regulation, Organization, and Memory)	Survivors with neurocognitive problems in task efficiency (RR = 0.77, 95% CI = 0.72–0.84) were less likely to meet CDC guidelines for physical activity
Miki, 2014	To demonstrate the feasibility and efficacy of speed feedback therapy with a bicycle ergometer on cognitive function in elderly cancer patients	RCT Intervention: speed feedback therapy with bicycle ergometer 1x week for 4 weeks	Elderly cancer patients (breast or prostate), > 70 years old Intervention group (n=38) Control Group (n=40)	Physical activity (participation in intervention)	Frontal lobe function (Frontal Assessment Battery)	Mean score of Frontal Assessment Battery for the intervention group was higher than that for the control group at week 4, mean of 16.61(1.37) compared to 14.95 (2.25), (p<.01)
Myers, 2015	To explore potential factors associated with perceived cognitive impairments in BCS compare to controls	Cross sectional	BCS Stage I-IV (n=317) 53.1-62.3 (majority stage II) Healthy controls (n= 46)	Exercise (Type, frequency, and duration of current exercise)	Perceived Cognitive Function (AFI; FACT-Cog)	Exercise moderated the negative effect of BMI on perceived cognitive impairments in the chemo group (F (3,133)= 3.1, p=.03)
Myers, 2012	To provide an in depth description of the experience of chemo-related cognitive impairment for women with breast cancer	Qualitative Descriptive (Qualitative Content Analysis) Focus Group & Semi structured interviews	BCS (n=18) 25-65 years old Stage I-IV Chemo (100% anthracycline and cyclophosphamide)	Exercise	Perceived global cognition	11/18 participants reported that exercise was beneficial to their cognitive function

Table 2.5 (continued)

Pradhan, 2014	To test the hypothesis that lower self-reported attention function in BCS would be associated with less exercise and higher BMI	Cross sectional	505 young BCS (45 years or younger at diagnosis and 3–8 years post-treatment) with 466 acquaintance controls	Physical activity (binary indicator of having regularly performed any of the following activities over the past 3 months)	Self report attention (AFI)	Controlling for fatigue, depression, and anxiety, better attention function was associated with a greater likelihood of exercise in the past 3 months (*b*=.106, *p* = 0.039)
Sleep Quality						
Oncology Populations						
Alvarez, 2013	To explore EEG biofeedback as a potentially restorative intervention for post chemo cognitive impairments in BCS	Pilot Study Quasi-experimental Participants served as own wait list control	BCS with self reported cognitive impairments (n=23) > 40 years who had chemo	Sleep (PSQI)	Cognitive functioning (FACT-COG)	Significant negative correlation between FACT-Cog quality of life subscale and PSQI sleep quality subscale (*r*= -.56, *p*<.01) Significant negative correlation between FACT-Cog quality of life subscale and PSQI- sleep daytime dysfunction (*r*=.42, *p* <.05)
Caplette-Gingras, 2013	To assess the relationship between insomnia and cognitive functioning	Cross-sectional	French-speaking women with non-metastatic breast cancer (N=67) Insomnia group (n= 47) Good sleepers group (n= 16)	Sleep (ISI, Daily Sleep Diary for 2 weeks)	Cognitive Performance (RCFT, (Weschler), RAVLT, TMT A/B Verbal Fluency Delis & Kaplan, PASAT, Color Word Interference Test, Spatial Span (Wechsler) Digit Span (Wechsler), Selective	Significant difference in verbal episodic memory domain (*p* =.004) in those with insomnia compared to good sleepers Those with insomnia symptoms performed significantly worse on the immediate recall and delayed recall tasks for logical memory and verbal episodic memory (*d*=.88) than the good sleepers Significant between group difference on executive functioning (*p*=.02, effect size *d*=.7) between insomnia group and the good sleepers No significant difference between insomnia and good sleepers on visual

Table 2.5 (continued)

					Attention Test Cognitive Function (CFQ))	episodic memory or attention and processing speed domains No significant difference on CFQ between insomnia group and the good sleepers Significant age X insomnia interactions found in executive functioning
Chen, 2012	To explore the changes in perceived attention function in women with breast cancer over time (2 years)	Prospective observational study (12 time points from before surgery to 24 months after)	Newly diagnosed breast cancer patients (n=200), stage I-IIIb 83% received chemo	Sleep (GSDS)	Perceived Attention (AFI)	Perceived attention function declined in 54% of women at 1 month after surgery 41% and 30% of women perceived attention decline at one and two years post surgery Perceived attention function related to sleep disturbance (r=-.43 to -.64, p<.01) across time
Hartman, 2015	To assess the relationship of obesity, physical activity, and sleep, with cognitive functioning among BCS	Cross Sectional	BCS, stages 1-3 (N= 136) Mean age 62.6 years (6.6), 65% received chemo	Total number of hours per night of sleep (self report)	Cognitive performance on memory, executive function, visual–spatial processing, verbal function, attention, information processing speed, and motor skills	More hours of sleep per night significantly associated with better performance on the verbal functioning domain (β = 2.69, SE = 0.98, p = 0.007)
Sanford, 2014	To examine symptom cluster based on concurrent and correlated symptoms in women receiving	Secondary analysis of longitudinal prospective study	BCS (n=80) undergoing chemo Age 49.7 (9.2) Stage I-III	Sleep (PSQI)	Perceived Cognitive Function (FACT COG)	PSQI and FACT-COG, moderately - highly correlated across 3 times points (p<.01) *Individual correlations not provided by author*

Table 2.5 (continued)

	treatment for breast cancer					
Mathews 2014	To examine the effect of CBT for insomnia on sleep improvement, daytime symptoms, and quality of life (QOL) in BCS after cancer treatment	Prospective RCT	Women who completed treatment for breast cancer stages I-III I (n=30) C (n=30)	Sleep (sleep-wake diary ISI)	Cognitive function (Cognitive function subscale EORTCQ-30, AFI)	In the cognitive behavioral group for insomnia, trend towards significance found for cognitive function improvement as insomnia symptoms improved (*p*=.07)
Mehlsen, 2009	To examine if cancer patients receiving chemo differ in cognitive changes during treatment from cardiac patients and healthy controls	Prospective observational T1 (0-7 days before chemo) T2 (4-6 weeks after last cycle of chemo	Breast cancer patients receiving chemo (n=34) Age 48.6 (8.0) Cardiac patients (n=14) Healthy controls (n=17)	Sleep quality (PSQI)	Cognitive Performance (WAIS-III, Digit span Forward and Backward, Stroop Test, RAVLT, WMS-III, RCFT immediate and delayed, Word Fluency-animals, "f", "n"	Sleep quality was not a significant predictor of cognitive decline across groups at baseline
Minton, 2012	To examine differences in objective cognitive function, activity levels and sleep in disease-free women who do and do not meet criteria for cancer-related fatigue syndrome	Cross sectional	BCS 3 months and 2 years after completion of any primary therapy (N=114) Divided into non fatigued and fatigued	Sleep (ISI; Actigraphs for 1 week)	Cognitive performance: (Paired Associates Learning, Rapid Visual Information Processing, Match to Sample Visual Search, Verbal Recognition Memory,	Significant between groups differences in insomnia prevalence— fatigued group had higher rates (44% vs. 16%; *p*=0.001) Significant between groups differences in mood (anxiety and depression)— fatigued group had higher scores (14.8 vs. 7.3, *p*<.001) In objective cognitive testing the fatigued group performed significantly worse than the non fatigued group on

Table 2.5 (continued)

					Delayed Matching to Sample, Affective Go No-go, Intra-Extra Dimensional Set Shift)	tests of sustained attention, reaction time and verbal memory (all $p<0.03$)
Myers, 2015	To explore potential factors associated with perceived cognitive impairments in BCS compare to controls	Cross sectional	BCS (n=317) Mean ages range 53.1-62.3 Stage I-IV Healthy controls (n= 46)	Sleep disturbance (MD Anderson Symptom Inventory)	Perceived Cognitive Function (AFI; FACT-Cog)	In the chemo group: Perceived cognitive impairments were associated with sleep disturbance (r = -.32, $p<.0001$)
Myers, 2012	To provide an in depth description of the experience of chemo-related cognitive impairment for women with breast cancer	Qualitative Descriptive (Qualitative Content Analysis) Focus Group & Semi structured interviews	BCS (n=18) 25-65 years old Stage I-IV Chemo	Perceived Sleep	Perceived global cognition	Participants described that periodic naps (or rest) throughout the day helped to sharpen their focus
Von Ah 2015	To examine relationships among the FACT-Cog scale, objective cognitive performance; and other symptoms (fatigue, depression, anxiety, and sleep disturbance)	Cross sectional	88 BCS who were on average 56.7 (SD 8.5) years old and 5.3 (SD 4.1) years post-treatment	Sleep (PSQI)	Cognitive Function (FACT-Cog) Cognitive Performance: RAVLT, Rivermead Behavioral Memory Test; SDMT; COWAT	The perceived cognitive impairments and perceived cognitive abilities were both significantly associated with depressive symptoms, fatigue, and anxiety Only perceived cognitive impairments was related to poor global sleep quality Sleep was significantly ($p<.05$) correlated with perceived cognitive function (r=.31); perceived cognitive impairments (r=.29)

*Note***. MCI**, Mild Cognitive Impairment

Table 2.5 (continued)

Inflammatory Factors: **TNF- α**, Tumor Necrosis Factor alpha; **BDNF**, Brain-derived neurotrophic factor; **IL-6**, interleukin 6
Self Report Scales: **AAHPERD**, American Alliance of Health and Physical Education Recreation and Dance; **AFI**, Attentional Function Index; **BAI**, Beck Anxiety Inventory; **CFQ**, Cognitive Failures Questionnaire; **CSC-W59**, Cognitive Symptom Checklist Work-59; **FACT-COG**, Functional Assessment of Cancer Treatment Cognition; **EORTC-CFS**, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 version 3.0; **FEDA**, **GHQ-12**, General Health Questionnaire- 12; **GSDS**, General Sleep Disturbance Scale; **GLT-EQ**, Godin Leisure Time- Exercise Questionnaire; **HADS**, Hospital Anxiety Depression Scale; **IPAQ**, International Physical Activity Questionnaire; **ISI**, Insomnia Severity Index; **MASQ**, Multiple Ability Self-Report Questionnaire; **MMQ**, Memory Questionnaire Ability Scale; **MoCA**, Montreal Cognitive Assessment; **PANAS**, Positive and Negative Affect Schedule; **PAOFI**, Patient's Complaints of Own Functioning Inventory; **PSQI**, Pittsburgh Sleep Quality Index; **VAS**, Visual Analogue Scale
NP Tests: **COWAT**; Controlled Oral Word Association Test; **CVLT-II**, California Verbal Learning Test; **D-KEFS**, The Delis–Kaplan Executive Function System; **HVLT-R**, Hopkins Verbal Learning Test Revised; **MMSE**, Mini Mental State Exam; **PASAT**, Paced Auditory Serial Addition Test; **RAVLT**, Rey Auditory Verbal Learning Test; **RCFT**, Rey Complex Figure Test; **SDMT**, Symbol Digit Modalities Test; **TMT A/B**, Trail Making Test A or B; **WAIS-III**, Wechsler Adult Intelligence Scale 4th edition; **WCST**, Wisconsin Card Sorting Test; **WMS III/ WMS-R**, Wechsler Memory Scale III/ Revised

studies, BCS associated their exercise behaviors with improved cognitive functioning (Cheung et al., 2012; Myers et al., 2012). Taken together, this review highlights the likely relationship between physical activity and cognitive function in BCS; however, the measurement of physical activity across these studies is questionable. More research is needed on physical activity and cognitive function using valid and reliable measures of self-reported physical activity.

Sleep Quality and Cognitive Function

The concept of sleep quality includes sleep disturbance and is related to insomnia. It is known that insomnia can negatively impact cognitive functioning. It has been consistently reported that those with insomnia have more cognitive difficulties and exhibit significant impairments on tasks assessing episodic memory (ES=0.51), problem solving (ES=0.42), working memory manipulation (ES=0.42), and working memory retention (ES= 0.22; Fortier-Brochu, Beaulieu-Bonneau, Ivers, & Morin, 2012). Neuroimaging data indicates that the prefrontal cortex region is vulnerable to the effects of sleep loss; however, behavioral data utilizing executive function tasks does not always support this (Killgore, 2010). Evidence suggests a relationship between insomnia and increased risk for development of neurodegenerative disorders and different dementia types (Yaffe et al., 2014). One of the proposed mechanisms for how sleep disturbances, such as insomnia, increase one's risk for dementia is through inflammatory pathways (Yaffe et al., 2014).

Even though results are mixed, there is a general consensus that poorer sleep quality in older adults is related to worse cognitive outcomes (Yaffe et al., 2014). Furthermore, there is evidence that sleep loss affects specific aspects of higher-level cognitive capacity and emotional regulation beyond global cognitive effects (Killgore, 2010; Walker 2010; Whitney & Hinson, 2010). In older adults, better sleep quality

measured both objectively with polysomnography and subjectively with questionnaires or sleep diaries, is associated with better global cognitive function, memory, and attention (Bastien et al., 2003; Fortier-Brochi & Morin, 2013). One study did not find such associations (Sivertsen, et al., 2013).

A literature review of primary research on sleep quality and cognitive function in breast cancer populations was performed in PubMed from 2005 to 2015. Eleven studies were identified, therefore, the population parameter was not expanded to all oncology populations. First, a search of these variables was conducted using the key words: sleep, sleep initiation and maintenance disorders, insomnia, cognitive function, cognitive dysfunction, cogniti*, cognitive decline, and breast cancer. Studies that included data on relationships between sleep quality and cognitive function in the identified populations were included. Animal and in vitro studies, studies evaluating risk for developing breast cancer, and pharmaceutical clinical trials were excluded and the findings are reported in in Table 2.5.

Summary

In breast cancer patients and survivors consistent relationships between aspects of sleep quality and cognitive functioning (both perceived and performance-based) were reported— specifically, between sleep quality (Sanford et al., 2014; Von Ah & Tallman, 2015), daytime functioning (Alvarez, 2013), sleep disturbance (Chen, Miaskowski, Liu, & Chen, 2012; Myers et al., 2015) and cognitive function. Insomnia symptoms were also consistently related to poorer cognitive functioning in episodic memory, immediate and delayed memory, executive function (Caplette-gringras et al., 2013; Mathews et al., 2014) but not consistently with attention and processing speed (Caplette-gringras et al., 2013; Minton & Stone, 2012). Hartman et al, (2015) reported that more hours of sleep per night was significantly associated with better verbal functioning on cognitive

performance measures. Only one study of BCS reported non-significant relationships between sleep quality and cognitive performance measures (Mehlsen et al., 2009). Across the reviewed studies, the Pittsburgh Sleep Quality Index is the most consistently used valid and reliable measure of self-reported sleep. There was heterogeneity across studies in terms of NP tests that were used to evaluate cognitive performance, making it difficult to draw conclusions regarding the specific cognitive domains that are related to sleep. More research is needed to better understand the nuances of the relationships between cognitive function and aspects of sleep quality—onset, duration, interference, and daytime sleepiness.

CHAPTER SUMMARY

Cognitive problems may persist for many BCS months to decades after chemotherapy ends; however, the exact mechanism of CRCI following the end of adjuvant therapy remains unclear. The most recent research on CRCI in BCS has linked inflammation to cognitive function both during and immediately following treatment (Cheung et al., 2014, Ganz et al., 2013; Kesler et al., 2013; Janelsins et al., 2012). However, inflammatory factors need to be evaluated in survivors 6 months to ten years after chemotherapy to better understand whether inflammation contributes to cognitive function after recovery (or partial recovery) occurs. Additionally, modifiable psychosocial (stress, social isolation) or behavioral (physical activity, sleep quality) factors that may also be directly or indirectly (through inflammatory mediators IL-6 and TNF-α) contributing to cognitive function have not been evaluated in BCS.

Psychosocial (stress, social isolation) and behavioral (physical activity, sleep quality) factors have been associated with both inflammation (IL-6, TNF-α) and cognitive function (memory, attention, processing speed, executive function) in the general and elderly populations and there is preliminary evidence in the oncology

literature that supports these relationships as well. However, the relationships of these constructs have not been examined *simultaneously* in BCS 6 months to ten years after treatment. The next logical step is to examine these relationships through a biobehavioral theoretical lens to provide foundational evidence for future prospective research studies and targets for behavioral interventions. This dissertation study is a critical first step in filling this gap in the literature, intended to both improve scientific knowledge of modifiable factors influencing inflammatory mechanisms of cognitive dysfunction and to provide essential information needed for developing interventions to improve cognitive function for BCS.

Chapter 3: Methods

This chapter provides the design, study procedures (sampling approach, measurement and instrumentation for data collection), and data analyses for the study. Procedures for protecting human subjects are also detailed.

DESIGN

The goal of this nonexperimental, cross-sectional study was to determine whether stress, perceived social isolation, physical activity, sleep quality, and inflammation are significant predictors of cognitive function in BCS (six months to 10 years following chemotherapy) and whether inflammation mediates the effects of these psychosocial and behavioral factors on cognitive function. Although this design is limited because it does not allow for the determination of causality, it does allow a large amount of data to be collected and is an appropriate way to explore the strength and quality of relationships among variables (Polit & Beck, 2011).

STUDY PROCEDURES

Prior to recruitment and enrollment, all study instruments and procedures were approved by the University of Texas at Austin Institutional Review Board. See Appendix A for approval letter.

Sample

Seventy-Five BCS who were 6 months to ten years post chemotherapy were recruited for this study. A linear multiple regression (fixed model, R^2 increase) power analysis was conducted in G*Power 3.1 to determine an appropriate sample size for the analyses in Aims 1 and 2. An effect size of f^2=0.21, two-tailed α = .05, power of 0.80, five tested predictors (those entered after covariates), and 12 total predictors (covariates and predictor variables) yielded a sample size of 68. The Principal Investigator (PI)

oversampled by 7 participants for a total sample size of 75 to compensate for missing or incomplete data and to allow for exploratory analyses in Aim 3. The effect size was determined based on the published significant relationship between TNF-α and IL-6 and verbal memory performance in BCS (Hopkins Verbal Learning Test-Revised [HVLT-R]: beta = -2.46, p=.006; Kesler, Janelsins, Koovakkattu, Palesh, Mustian, Morrow, & Dhabhar, 2013).

The sample of BCS was recruited primarily from the greater Austin, TX metropolitan area from May 1, 2016 through January 16, 2017. The Austin metropolitan area comprising over 1.8 million people as of 2010: 54% Non-Hispanic white, 32% Hispanic, 6.9% Black, 7.1% other ("Texas Population", 2014). In 2009, the number of female Texans with a diagnosis of breast cancer in the previous 10 years was 98,038 (592 men were also diagnosed with breast cancer) and the 5-year survival rate for those diagnosed in 1995-2009 for all races/ethnicities and stages of breast cancer was 86.5% (Risser et al., 2012). As of 2011, there were 3,725 women living with a history of breast cancer stages I-III living in the greater Austin, TX metropolitan area—73.7% Non-Hispanic white, 7.4% Black, 14% Hispanic, and 2.3% Asian/Pacific Islander (Risser, 2014).

The sample was also recruited nationally, through The Army of Women program (AOW). The AOW is part of the Dr. Susan Love Research Foundation, a not-for-profit California corporation. The AOW unites researchers with women and men willing to participate in research studies related to breast cancer. The AOW enables women and men of all ages, ethnicities and levels of breast cancer risk to volunteer to participate in research studies focused on understanding the means to prevent breast cancer before it starts. There are currently over 380,000 members in the AOW database, 1517 of which registered in the Austin area. The AOW's scientific advisory council reviewed this study

protocol and approved this study to be broadcasted to the Army of Women database and listed on the armyofwomen.org website (See Appendix B for AOW Approval Letter). The AOW assisted with content development of an e-blast letter (See Appendix C for the E-blast Letter) that was sent to the entire AOW national database. Those AOW volunteers who were interested contacted the AOW staff directly and the AOW staff sent the PI a weekly email with the contact information for those interested AOW members. Additionally, the AOW posted the study information on their website throughout the life of the study.

Inclusion Criteria

All participants were female, with a history of breast cancer (stage I-III) that received chemotherapy as part of their treatment, and have been without cancer recurrence or secondary cancers for six months to 10 years. Women currently receiving hormonal therapy were included. Participants were between the ages of 21 to 65 years old, able to read and write in English, and of any ethnic/racial group.

Exclusion Criteria

Women older than 65 were excluded to control for age-related cognitive decline (Aartsen, Knipscheer, Smits, & Deeg, 2002). Women on systemic steroids (in the previous month) or biologic response modifiers, those with a history of inflammatory breast cancer, women with physician diagnosed inflammatory diseases (diabetes mellitus, rheumatoid arthritis, autoimmune diseases) or pre-cancer history of sleep disorders, severe insomnia, severe cognitive impairments (diagnosed by a physician), a verbal learning disability, or other neurological or psychiatric disorders that can impact cognition or emotions and interfere with completion of questionnaires were also excluded. These criteria were outlined in the pre-screening form.

Recruitment and Screening

Participants were recruited through community oncology centers (Texas Oncology [TxO]; 80% of cancer patients and survivors receive healthcare in these settings, Richardson & Tangka, 2007), a breast cancer patient and survivor navigation center that serves the greater Austin metropolitan area (Breast Cancer Resource Center [BCRC]), over 200 oncology nurses who are members of the Central Texas Oncology Nursing Society (CTONS), the Army of Women (AOW, a national non-profit that recruits women with and without breast cancer who are interested in being involved in breast cancer research; https://www.armyofwomen.org), and through social networking within the Austin community. TxO posted flyers in their clinics and allowed the PI to educate clinicians in person on the inclusion/exclusion criteria. The BCRC allowed the PI to educate their patient navigators in person on the inclusion/exclusion criteria and provided study information to survivors at support groups and online twice a month throughout the life of the study. The PI also presented her study and provided recruitment flyers to CTONS members. The AOW sent out an E-blast email to all members nation wide with detailed study information and posted the study information on their website. Additionally, if someone in the community expressed interest in the study, the PI provided her business card and a recruitment flyer to the interested person. The recruitment flyer clearly stated the study's purpose, the expectations for participants, eligibility requirements, the investigator's contact information, and the University of Texas IRB protocol number (Appendices D, E, F, and G for Letters of Support and the Recruitment Flyer).

Potential participants were screened for eligibility via the telephone (Appendix H). A prescreening form was used to ensure that participants were eligible to participate in the study based on the inclusion and exclusion criteria. If eligible, the participant's

willingness to participate and verbal consent were obtained. Consent forms were sent to participants via mail or email depending on the participants' preferences (Appendix I).

One hundred and nine women were screened for this study. Of these, 21 did not meet study inclusion criteria. Six had a history of stage IV breast cancer, nine did not complete chemotherapy within the outlined timeframe (six months < chemo completion date < 10 years). Four women had a history of inflammatory comorbidities or other comorbities that interfere with normal cognitive processes. One woman was older that 65 years, and another was on steroid treatment. Of the 88 women who met the inclusion criteria, two lived too far away to participate, and 11 did not respond to scheduling attempts. Thus, 75 women were enrolled in the study from April 2016— January 2017. The PI was unable to successfully access the veins on nine of the participants due to lymphedema, sclerosed veins, or other anatomical reasons. Therefore, blood samples were obtained from 66 of the 75 participants. The final sample used for the primary aims of this study was 66 for aims 1 and 2, and all 75 were used for aim 3 and in additional exploratory analyses.

Data Collection

All data was collected specifically for this research project. The data included questionnaire responses, anthropometric measures, standardized NP tests, and blood. This data allowed for the measurement of demographic and disease and treatment-related factors; stress, perceived social isolation, physical activity, and sleep quality; inflammatory markers (IL-6, TNF-α); and cognitive function (memory, attention, processing speed, and executive function performance, perceived cognitive function). See Appendix J for all the Study Instruments. Once participants completed a phone screening and verbal consent, an appointment was scheduled for a day that was convenient for the participant. Data collection appointments were scheduled 1-4 hours after they woke up

that morning. Prior to the scheduled appointment, participants were mailed/or emailed a written consent form and a link to Part 1 of the structured questionnaire (Perceived Stress Scale [Cohen, Kamarck, & Mermelstein, 1983], UCLA-R Loneliness Scale [Russel, 1996], Pittsburgh Sleep Quality Index [Buysse, Reynolds, Monk, Berman, & Kupfer, 1989], PROMIS Item Bank v1.0 – Emotional Distress – Anxiety – Short Form 8a, PROMIS Item Bank v1.0 – Emotional Distress – Depression – Short Form 8a, PROMIS Item Bank v1.0 – Fatigue – Short Form 8a [http://www.healthmeasures.net/explore-measurement-systems/promis]. They returned the consent and Part 1 of the questionnaire prior to or at a scheduled appointment at the UT School of Nursing Family Wellness Center.

Face-to-face data collection included anthropometric assessment (weight, height, waist circumference, hip circumference) and standardized NP testing by the PI (Hopkins Verbal Learning Test Revised [Benedict, Schretlen, Groninger, & Brandt, 1998], Trail Making Tests A and B [Tombaugh, 1994], Controlled Oral Word Association Test [Benton, & Lester, 1994]). The PI was properly trained to perform and analyze the NP tests and was supervised by her dissertation members, Dr.'s Heather Becker and Shelli Kesler, during data collection. During the period of time needed to perform the delayed section of the HVLT-R, Part 2 of the structured questionnaire was administered (demographic questions, Charlson Comorbidity Index [Charlson, Pompei, Ales, & MacKenzie, 1987], International Physical Activity Questionnaire [Craig et al., 2003], and Epworth Daytime Sleepiness Scale [Johns, 1991]). Non-fasting blood samples were drawn by the PI for all participants between 1-4 hours of waking to control for potential circadian variation. Ten milliliters of blood was taken from a vein [e.g. antecubital area, metacarpal plexus, dorsal venous arch, etc.) per standard operating procedures using aseptic technique and a butterfly needle blood collection set (See Appendix K for

standard operating procedure). Blood was collected into 10 ml serum separator tubes (BD Franklin Lakes, New Jersey) and allowed to clot at room temperature for 30 min – 2 hr per the manufacturer's instructions. Data collection required approximately 60 minutes per participant.

Protection of Human Subjects

The University of Texas at Austin Institutional Review Board approved all study procedures and forms prior to the initiation of recruitment and enrollment. Potential participants were screened for eligibility via the telephone. If eligible, the participant's willingness to participate and verbal consent were obtained. A written consent was provided and explained to participants via email or mail per participant preference. It was emphasized that participation was voluntary and they could withdraw at any time.

Each participant was assigned a unique identification number and the list linking the individuals' names and addresses to the ID number was kept on the investigator's encrypted laptop in a password-protected file. Confidentiality of data records was maintained by keeping signed consent forms separate from data files in locked cabinets in the Dissertation Chair's research office. Only the PI and her dissertation chair have access to the password-protected file. All data from participants were entered into the separate computer that houses the data under a high-security password interface. All research computers are encrypted, with secure university back up for all files.

The PI wrote the assigned record number on completed questionnaires and NP testing materials and placed them in the locked file cabinet, in a locked office, within the School of Nursing that has a security guard on duty whenever the front door is open. The PI only worked with questionnaires with code numbers, not names. All the blood samples, instruments and lab specimens were labeled with the assigned code numbers. Hard copies of the questionnaires are kept in a locked file cabinet in a locked research

office in a locked campus building. Electronic copies of the electronic surveys (with unique id numbers) are kept within the University of Texas Qualtrics secured, cloud-based database. Blood samples are stored in a freezer in the BioBehavioral Lab, which is a locked lab. Written questionnaire data will be kept for 5 years after publication of all findings and then destroyed according to university policies— written documents will be shredded. Blood samples will be kept five years after study publications and then disposed of in biohazard containers according to University Environmental Health and Safety policies.

The data or samples was only shared with members of the PI's Dissertation Committee who supervised the conduct of this research project, and have not been shared with other researchers for purposes not detailed in this study. Data were not anonymous but will be kept confidential through the use of numerical identifiers.

MEASUREMENT AND INSTRUMENTS

A summary of the instruments used in this study can be found in Table 3.1 Summary of Study Instruments.

Individual Factors and Demographics

Demographic Variables

An information sheet was used to collect demographic information (age, education, race, ethnicity, marital status, income, employment) as well as information on disease and treatment (type of breast cancer, type of cancer treatments, date of chemotherapy completion, current medications, comorbidities, menopausal status, and genetic testing information). These data were used to describe the sample and in the selection of covariates.

Table 3.1.

Summary of Study Instruments

Instrument	Abbreviation	Variable(s)	Subscales	# of Items	Range Meaning	Reported Reliability and Validity
PROMIS Item Bank v1.0 – Emotional Distress – Anxiety – Short Form 8a (http://www.healthmeasures.net/explore-measurement-systems/promis)	PROMIS Anxiety	Anxiety related feelings in the last 7 days	N/A	8	8-40, higher scores indicate more anxiety and distress	(α's >0.95; Wenzel et al., 2015)
PROMIS Item Bank v1.0 – Emotional Distress – Depression – Short Form 8a (http://www.healthmeasures.net/explore-measurement-systems/promis)	PROMIS Depression	Depressive Symptoms in the last 7 days	N/A	8	8-40, higher scores indicate more depressive symptoms	(α's >0.95; Wenzel et al., 2015) Validated in breast cancer patients (Teo, Novy, Chang, Cox, & Fingeret, 2015)
PROMIS Item Bank v1.0 – Fatigue – Short Form 8a (http://www.healthmeasures.net/explore-measurement-systems/promis)	PROMIS Fatigue	Feelings of Fatigue in the last 7 days	N/A	8	8-40, higher scores indicate more fatigue-related symptoms	(α's >0.86; Cessna et al., 2016 Validated in women undergoing adjuvant treatment for breast cancer (Junghaenel, Cohen, Schneider, Neerukonda, & Broderick, 2015)
Perceived Stress Scale (Cohen, 1983)	PSS	Degree that life	n/a	10	0-40, higher scores indicate	Adequate reliability and

Table 3.1 (continued)

		circumstances are appraised as stressful in last 7 days			higher perceived stress	validity in breast cancer patients (α's ranged from .86 to .92; Golden-Kreutz et al., 2004
UCLA-Loneliness Scale Revised V. 3 (Russell, 1996)	UCLA-R	Perception of lack of social connectedness, or loneliness in last 7 days		20	Higher scores indicate greater degrees of loneliness	Validated in BCS Adequate reliability (α=0.89; Fogel, Albert, Schnabel, Ditkoff, & Neugut, 2002)
International Physical Activity Questionnaire Long Version (Craig et al., 2003)	IPAQ	Self-report recall of the frequency of various forms of physical activity in the last week		27	Total minutes of participation in physical activity in the last 7 days	Repeatability coefficient of 0.81 (Craig et al., 2003)
Pittsburgh Sleep Quality Index (Buysse, 1998)	PSQI	Subjective reports of sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction in the last week	7: Sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction	19	0-21, higher scores indicate worse sleep quality	Evaluated in cancer patients (α=0.81; Sprod, Palesh, Janelsins, Peppone, Heckler, Adams… Mustian, 2010)
Epworth Sleepiness Scale	ESS	Daytime	N/A	8	0 to 24, higher	Evaluated in

Table 3.1 (continued)

(Johns, 1991)		sleepiness			scores indicate more daytime sleepiness	breast cancer patients (α=0.78-.79; Enderlin et al., 2011).
HVLT-Revised Immediate and Delayed (Benedict et al., 1998)	HVLT-I HVLT-D	Auditory Verbal Learning		Immediate Recall: 3 Trials Delayed Recall: 1 Trial	12 words on the list	Test/retest correlation for the HVLT-R delayed subscale was .66 (McDougall, Becker, Acee, Vaughan, & Delville, 2011)
Trail Making Tests A & B (Tombaugh, 2004)	Trails A Trails B	Processing speed, executive function, attention, and cognitive flexibility		2 Trials	A: 25 circles of numbers B: 25 circles of numbers and letters	Reliability coefficients 0.89 and 0.92 (Mitrushina, Boone, & Razani, 2005)
COWAT (Wefel et al., 2011)		Verbal Fluency	N/A	1 Trial	3 letters (F,A,S)	Reliable and generally stable over time (α 0.82 and test retest coefficient 0.74 (Ruff, Light, Parker, & Levin, 1996)
Functional Assessment of Cancer Therapy-Cognitive Function Instrument version 3 (Wagner et al.,	FACT-Cog PCI PCA	Perceived Cognitive Dysfunction in the past 7 days	4: perceived cognitive impairments, impact on	34	0 to 148; higher scores indicate better cognitive	4 sub-scales reliable (α's=0.67-0.94) when used for BCS 6 months

Table 3.1 (continued)

2009)	quality of life, comments from others, and perceived cognitive abilities	function and quality of life	after chemotherapy (Wagner, Sweet, Butt, Lai, & Cella, 2009)

Body Mass Index (BMI)

BMI was measured because inflammatory markers including IL- 6, TNF-α, IL-8, IL-18, and IL-1ra are consistently associated with obesity indices in large population-based studies (O'Connor et al., 2009). Height was measured to the nearest 0.5 cm with participants' back to the wall, without shoes, looking straight ahead. All participants' were weighed with the same digital scale (Tanita Model WB-300 Plus Arlington Heights, Illinois) to the nearest 100 g, wearing no shoes and light clothing. BMI was calculated using weight in kilograms and height in cm. Waist circumference was measured (in cm) between the 12th rib and the iliac crest, and the hip circumference was measured (in cm) around the buttocks at the maximum extension according to the World Health Organization ("Waist circumference and waist–hip ratio: report of a WHO expert consultation", 2008) and the hip to waist ratio (HWR) will be calculated. A ratio of 0.8 or greater is considered a measure of central adipose tissue.

Illness and Treatment related Variables (Tamoxifen-use and History of Anthracycline based chemotherapy)

Tamoxifen use was determined using a dichotomized variable of history of tamoxifen use or no history. History was determined from participants' answer to the following question on the information sheet, "What treatments are you presently using for your breast cancer treatment?". Answer choices included: no medications, steroids, aromatiase inhibitors (e.g. Arimidex®, Aromasin®, Femara®), selective estrogen receptor modulators (e.g. tamoxifen, Evista®, Fareston®), Estrogen receptor down regulators (e.g. Faslodex®), or other. History of anthracycline-based chemotherapy was determined by using a dichotomized variable of history of anthracycline treatment or no history. History was determined from the following question included in the information

sheet that asks, “What types of treatments did you receive for your breast cancer treatment? Circle all that apply.” Answer choices for chemotherapy types included anthracycline (Adriamycin, Doxil, doxorubicin); methotrexate (Amethopterin, Mexate, Folex); paclitaxel (Taxol); docetaxel (Taxotere); fluorouracil, 5-fluorouracil, 5-FU (Adrucil); carboplatin (Paraplatin); and cyclophosphamide (Cytoxan).

Psychosocial Factors

Emotional Distress

Emotional Distress, defined in this study as depressive and anxiety related symptoms, was measured using two PROMIS© scales, the Emotional Distress – Anxiety – Short Form 8a and Emotional Distress – Depression–Short Form 8a (Cella et al., 2010). PROMIS scales are designed to capture health related outcomes from patient perspectives and have undergone extensive psychometric evaluation within the National Institutes of Health (Cella et al., 2010). These scales are available on the NIH website (http://www.healthmeasures.net/explore-measurement-systems/promis).

The Emotional Distress- Anxiety Short form 8a is an 8-item scale that asks how often a person experienced anxiety related feelings in the past seven days. Answer choices range from 1 (“never”) to 5 (“always”) and total scores can range from 8-40 with higher scores indicated more anxiety related symptoms.

The Emotional Distress- Depression Short form 8a is an 8-item scale that asks how frequently a person experienced depressive feelings in the past seven days. Answer choices range from 1 (“never”) to 5 (“always”) and total scores can range from 8-40 with higher scores indicated more depressive symptoms. Both the Anxiety and Depression Short forms have demonstrated adequate reliability across populations, including cervical cancer survivors (α’s >.95, Wenzel et al., 2015) and the PROMIS Depression has been validated in breast cancer patients (Teo, Novy, Chang, Cox, & Fingeret, 2015).

Fatigue

Fatigue, defined in this study as perceived feelings of tiredness, was measured using the PROMIS Fatigue Short form 8a, an 8 item scale that asks how frequently a person experienced fatigue related feelings in the past seven days. Answer choices range from 1 ("not at all") to 5 ("very much") and total scores can range from 8-40 with higher scores indicating more fatigue related symptoms. This measure has demonstrated adequate reliability across populations (Cella et al., 2010), including cancer patients (α's >0.86, Cessna et al., 2016) and has been validated in women undergoing adjuvant treatment for breast cancer (Junghaenel, Cohen, Schneider, Neerukonda, & Broderick, 2015).

Stress

Perceived psychological stress was measured using the Perceived Stress Scale (Golden-Kreutz, Browne, Frierson, & Andersen, 2004), a 10-item scale measuring the degree that life circumstances are appraised as having been stressful in the previous week. Responses for each item range from 0 ("never") to 4 ("very often"). This measure has demonstrated adequate reliability and validity in breast cancer patients (α's ranged from .86 to .92; Golden-Kreutz et al., 2004).

Perceived Social Isolation

Perceived social isolation, defined as loneliness, was measured using the UCLA-R Loneliness Scale version 3 Survey (Russel, 1996). This 20-item instrument quantifies how people experience their loneliness. Each item asks how often each feeling is experienced— answer choices are "never", "rarely", "sometimes", and "always" (Russell, 1996). Higher scores indicate more loneliness and perceived isolation. The UCLA-R Loneliness Scale, used widely, has been validated in breast cancer survivors

and has demonstrated adequate reliability (α=.89; Fogel, Albert, Schnabel, Ditkoff, & Neugut, 2002).

Behavioral Factors

Physical Activity

Physical activity was measured using a self-report recall of the frequency of various forms of physical activity (job-related, transportation, household, recreation/leisure time, time spent sitting/sedentary time) in the last seven days using the International Physical Activity Questionnaire (IPAQ) long version. This 27-item instrument asks how many days in the last week certain physical activities have been performed—for example, "How much time do you usually spend on one of those days doing moderate physical activities as part of your work?" Participants' answers provide minutes per day and days per week. A domain-specific score for walking, moderate, and vigorous activities, as well as a total score of the metabolic equivalent (MET) can be estimated (for exact criteria see Scoring Protocol under http://www.ipaq.ki.se/scoring.pdf). The IPAQ is accepted worldwide as an adequate measure of physical activity in adults (repeatability coefficient of 0.81; Craig et al., 2003).

Sleep Quality

The operational definition of sleep quality for this study is subjective reports of sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction as measured by the Pittsburgh Sleep Quality Index (PSQI; Buysse, 1989). The PSQI is a self-administered 19-item questionnaire measuring quality of sleep over the past month, and has been successfully utilized to identify sleep disturbances in cancer survivors (Palesh et al., 2012). The PSQI evaluates seven aspects of sleep: subjective sleep quality, sleep latency, sleep duration, sleep

efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. Scores range from 0 to 21; lower scores indicate better sleep quality. The PSQI is a reliable measure of sleep quality in cancer patients (α=.81; Sprod, Palesh, Janelsins, Peppone, Heckler, Adams… Mustian, 2010). An additional measure of daytime sleepiness, the Epworth Sleepiness Scale (8-items), was used in this study to understand the effects of sleep quality on daytime sleepiness as it relates to cognitive functioning (http://epworthsleepinessscale.com/about-epworth-sleepiness/). Each item response choices are 0 to 3, with higher scores indicating greater daytime sleepiness. This measure has demonstrated reliability in breast cancer patients (α = .78-.79; Enderlin et al., 2011).

Inflammatory Markers (IL-6 & TNF-α)

Two markers of inflammation were chosen for this study based on preliminary (though inconclusive) evidence supporting their associations with problems with cognitive function in BCS, individual factors, psychosocial factors, and behavioral factors: interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These circulating markers were assessed from serum. The PI used venipuncture to collect non-fasting blood (10 ml) into serum separator tube vacutainers 1-4 hours after each participant woke in the morning. Samples were allowed to clot for 30 min- 2 hours at room temperature (per the manufacturer's instructions), then transported (in a portable cooler that maintained room temperature) to the University of Texas at Austin School of Nursing BioBehavioral lab (Biosafety Level 2 facility, EHS Approval # 2012-07-0096) that is located in the School of Pharmacy. In the lab, the samples were centrifuged at 3,330 rpm for 15 min, then serum was aliquoted using a filtered pipette into 1ml polypropylene tubes, and stored at -80°C according to environmental health and safety biohazard policies at UT.

Cognitive Function

Perceived Cognitive Functioning

Perceived cognitive function was measured with the Functional Assessment of Cancer Therapy-Cognitive Function Instrument version 3 (FACT-Cog), a 34-item self-administered questionnaire that measures how often cognitive dysfunction has been experienced in the last 7 days. Responses range from 0 ("never") to 4 ("several times a day"). The FACT-Cog is made up of 4 sub scales: perceived cognitive impairments, impact on quality of life, comments from others, and perceived cognitive abilities. Negatively stated items are reversed scored. Total scores can range from 0 to 148; higher scores indicate better cognitive function and quality of life. This instrument is often utilized in studies of breast cancer survivors' cognitive function and is a valid measure of cancer patients' perceived cognitive deterioration (Cheung et al., 2014). The 4 sub-scales were found to be reliable (α's = .67 - .94) when used for 204 breast cancer patients 6 months after chemotherapy (Wagner, Sweet, Butt, Lai, & Cella, 2009).

Cognitive Performance

The cognitive domains most affected in BCS are memory, attention, processing speed, and executive function. The International Cognition and Cancer Task Force recommends that the following well-established valid and reliable NP measures be used in cancer and cognition-related research: the Hopkins Verbal Learning Test-Revised (HVLT-R, a measure of verbal memory; Benedict et al. 1998), the Trail Making Test A and B (Trails A and B, a measure of processing speed, executive function, attention, and cognitive flexibility; Tombaugh, 2004), and the Controlled Oral Word Association Test (COWAT; a measure of verbal fluency and word finding; Wefel, Vardy, Ahles, & Schagen, 2011). The PI followed standardized testing protocols and administered these measures.

For the HVLT-R, participants were instructed to listen to a list of 12 words and repeat back as many of the words that they could remember. The list was repeated and participants asked to say as many words that they could remember included those they already said. This process was repeated a third time. For delayed recall, 20-25 min later, participants were asked to remember and say as many of the 12 words from the original list that they could one time. Finally, for forced recognition, participants were read a longer list of 24 words that included the original 12 words along with distractor words. Each word is read aloud and the participant says "yes" if the word was on the original list and "no" if it was not. In a study of older adult cancer survivors the test/retest correlation for the HVLT-R delayed subscale was .66 (McDougall, Becker, Acee, Vaughan, & Delville, 2011) and is sensitive to distinguish between breast cancer survivors who received chemotherapy from survivors who did not receive chemotherapy (Kesler et al., 2013).

For the Trail Making Test Part A, participants were first presented with a piece of paper that had a sample of 8 numbered circles and instructed to connect the numbers in ascending order (1, 2, 3, etc.) as quickly as possible. Their time in seconds was recorded. Then the paper was turned over and on the other side were 25 numbered circles and the participants were instructed to connect the numbers in ascending order (1, 2, 3, etc.) as quickly as possible. Their time in seconds was recorded. For the Trail Making Test Part B, participants are presented with a piece of paper that had numbered circles (1-4) and letters (A-D) and instructed to connect the numbers in ascending order (1-A-2-B-3-C, etc.) as quickly as possible. Their time was recorded in seconds. Then the paper was turned over and on the other side were more numbered circles (1-13) and letters (A-L) and the participant was instructed to connect the numbers in ascending order (1-A-2-B-3-C, etc.) as quickly as possible. Their time was recorded in seconds. For both trials, the

participants were watched and errors pointed out by the tester so that they could be corrected. This test has been accepted as valid measure for differentiating those with organic brain damage (e.g. brain tumor, penetrating head injury, closed head injury, cerebral vascular accident, cerebral abscess, cerebral atrophy, subdural hematoma) from those without damage for many years (Reitan, 1958) and has demonstrated adequate reliability (coefficients 0.89 and 0.92; Mitrushina, Boone, & Razani, 2005).

For the COWAT, participants were asked to name as many words they could think of (not proper nouns) that begin with the letter "F" over the course of 1 minute. This was repeated for letters "A" and "S". The tester wrote down the words as the participant said them out loud. This measure is reliable and generally stable over time (α .82 and test retest coefficient .74; Ruff, Light, Parker, & Levin, 1996).

DATA CLEANING AND CHECKING

All data were entered into SPSS 24.0 (IBM, 2016). First, data were cleaned—frequencies on each variable were run, and missing values checked for errors versus missing data. NP tests were scored following the instructions in the manuals. 100% of the NP data were audited—each test score was double-checked by another trained research assistant working in our research lab at the University of Texas at Austin School of Nursing. Ten percent of all the survey data were audited. Only 9 errors were identified out of 2064 potential values, which is equivalent to a 0.4% error rate, suggesting a low rate of random human error and minimal concern for systemic data entry errors.

DATA ANALYSES

Cytokines

Blood samples were collected, stored, prepared, and processed according to the manufacturer's protocol (EMD Millipore; Darmstadt, Germany, See Appendix L) under the supervision of committee member, Dr. Kesler. The serum aliquots were transferred

from the School of Nursing Biobehavioral Lab to the Health & Integrative Physiology Lab at the University of Texas at Austin and stored at -80 degrees Celsius.

Human high sensitivity T cell magnetic bead panel (multiplex) assays were used for the simultaneous quantification of IL-6 and TNF-α in participants' serum. These immunoassays utilize antigen-antibody reactions to quantify levels of biomarkers in serum. This process involved mixing beads were complexed with antibodies for either IL-6 or TNF-α with each participants' serum in separate wells of a 96-well plate. The complexed antibodies bound with the free floating antigens for IL-6 and TNF-α in the participants' serum while incubating overnight at 4°C. Following incubation, a second biotinylated "detection" antibody was added to each of the wells to form a 'sandwich' of antigen-antibody complexes. Since the antibodies were complexed to beads that were magnetic, a magnet was used to hold the beads at the bottom of the wells during subsequent washing steps to remove remaining serum and reagents. Then a streptavidin-phycoerythrin substrate was added to the wells so the antigen-antibody complexes could be visualized.

The 96-well plate was then run on a Luminex 200, which utilized flow cytometry, to determine the concentrations of analytes in the samples. The antigen-antibody complexes fluoresce and the instrument provided a Mean Fluorescent Intensity (MFI) value that correlated to the amount of analyte in the original sample. MFI values were provided for seven standards that were included with the kit. These standards were treated just like samples and are also run on the LUMINEX 200. Known concentrations were plotted against MFI units for each of the standards and a 5-parameter logistic regression was used to generate a line of best fit so that unknown concentrations could be determined. Additionally, two separate quality controls were run to ensure the validity of the multiplex assay kits and samples were run in duplicate in order to use an average

value for each person and increase the reliability. According to the manufacturer, there is no cross reactivity between the antibodies for the IL-6 and TNF-α analytes. The minimum detectable concentration for IL-6 is 0.11 pg/mL and for TNF-α is 0.16 pg/mL. The intra assay precision (%CV) for IL-6 is <5% and for TNF- α is <5%. The inter-assay precision (%CV) for IL-6 is <20% and for TNF-α is <15%.

Cognitive Performance

Cognitive function was the key dependent variable in this study and was operationalized as both cognitive performance and perceived cognitive function. Cognitive performance was measured with NP tests including the HVLT-R Immediate and Delayed, COWAT, TMT A&B. NP scores were converted to normalized scores (adjusted for age and years of education) for the purpose of better profiling and describing the sample.

Basic Assumption Checking and Univariate Analyses

All study variables were analyzed separately looking at assumptions of normality and identifying outliers— using central tendencies, histograms, box plots and statistics for kurtosis and skewness. If distributions of biomarkers were skewed, the log 10 transformation was utilized to normalize the data. In the event of missing data, mean substitution was used when the participant completed 80% or more of a given scale.

Assumption checking for Multivariate Analyses

The statistical assumptions for ordinary least squares regression were checked to ensure that the probability of rejecting the null hypothesis was not higher than the chosen significance level and power of this statistical analysis. The assumptions for correlation and regression based tests include normality, independence, linearity, and homoscedasticity. Normality was assessed for all the study variables to ensure that the errors in estimates of Y, or the dependent variable, were evenly distributed using

histograms with overlain normal distribution curves, skewness and kurtosis statistics, and Shapiro-Wilks Test. The independence assumption was logically assessed by the principal investigator's knowledge of participants. The linearity assumption was assessed using both correlation analyses and by examining scatter plots (when Y is plotted as a function of X). To evaluate whether the homescedasticity assumption was met, the standardized residuals were plotted with a line of best fit to ensure that the errors in estimation were equally variable conditioned on Y for each regression analysis. This is important because violations of this assumption impact inference through the effects on the standard error of the regression coefficient (Hayes, 2013).

Hypothesis Testing

Alphas were set at 0.05 for all analyses in this study. The following analysis plan was constructed to address the three study aims and adjusted as needed based on the study results:

Aim 1: To assess the impact of psychosocial (stress, perceived social isolation) and behavioral (physical activity, sleep quality) factors on inflammatory markers (IL-6, TNF-α). Several hierarchical multiple regression models (two-tailed, $p<0.05$) were intended to be used to determine the variance of inflammatory factors explained by psychosocial and behavioral factors after controlling for selected individual factors. The individual covariates were intended to be chosen based on the exploratory Pearson's correlations conducted during the univariate analyses. Those variables that had the largest correlations with cytokines and had the greatest degree of linearity were intended to be chosen as covariates in these analyses. The theoretical framework described in Chapter 1 in addition to the results from the correlation analyses scatterplot graphs, were intended to guide the predictor entry for each analysis.

Aim 2: To assess the impact of inflammatory markers (IL-6, TNF-α, IL-6*TNF-α) on cognitive function (memory, attention, processing speed, executive function performance, perceived cognitive functioning) after controlling for selected individual factors. Several Hierarchical Multiple Regression (two-tailed, $p<0.05$) were intended to be used to determine the variance in each measure of cognitive function (cognitive performance, perceived cognitive functioning) explained by IL-6 and TNF-α, and IL-6*TNF-α after controlling for selected individual factors. The theoretical framework described above in addition to the results from the correlation analyses scatterplot graphs were intended to guide the order of predictor entry for each analysis.

Aim 3 (exploratory): To explore direct and indirect (through inflammatory mediators IL-6 and TNF-α) effects of psychosocial (stress, perceived social isolation) and behavioral (physical activity, sleep quality) factors on cognitive function (memory, attention, processing speed, executive function performance, perceived cognitive function) after controlling for selected individual factors. The individual covariates were intended to be chosen based on the exploratory Pearson's correlations conducted during the univariate analyses. Those variables that had the largest correlations with both the cytokines and cognitive outcomes were intended to be used in these analyses as covariates. Simple mediation analyses using ordinary least squares path analysis was were intended to be used to explore the direct and indirect (through inflammatory mediators) effects of psychosocial and behavioral factors on cognitive function. Andrew Haye's PROCESS procedure for mediation analysis was utilized, because this method has advantages over the traditional causal steps approach—it is a more powerful statistical analysis (one-step hypothesis testing vs. three), and it allows for inferential quantification of the indirect effects on dependent variables through mediator variables (Hayes, 2013). This method utilizes bootstrap confidence intervals to estimate and

interpret the effect size of the indirect effects of the independent variables on the dependent variables. "Bootstrapping is less susceptible to the influence of outliers in small populations than other methods…and it doesn't rely on large sample asymptotics" (Andrew Hayes, PhD, personal communication, February 20, 2015). The direct effects of predictor variables on cognitive function were determined by the regression coefficient magnitude and significance ($p<.05$), and the indirect effect of the inflammatory markers was determined by a significant effect size (95% Bootstrap CI does not include "0").

CHAPTER SUMMARY

This non-experimental, cross-sectional study was an analysis of data from BCS six months to 10 years post chemotherapy. The goal of the study was to determine whether stress, perceived social isolation, physical activity, sleep quality, and inflammation are significant predictors of cognitive function and whether inflammation mediates the effects of psychosocial and behavioral factors on cognitive function. These variables were measured with valid and reliable measures. For study aims one and two, hierarchical regression were intended to be used to evaluate the variance in inflammation (or cognitive function) explained by modifiable factors above and beyond the individual factors. Exploratory analyses using ordinary least squares path analysis was intended to be used to explore the direct and indirect (through inflammatory mediators) effects of psychosocial and behavioral factors on cognitive function. The University of Texas at Austin Institutional Review Board approved all study procedures and protection of human subjects.

Chapter 4: Findings

Chapter 4 presents the results of this dissertation study. Data were extracted from survey questionnaires, NP test records, height, weight, hip and waist measurements, and immunoassay results and entered into SPSS 24.0 (IBM, 2016). The SPSS data file was proofread against the original data for accuracy by the principal investigator and a volunteer research assistant. The data cleaning and proofing procedures are described in full detail in Chapter 3. Descriptive statistics, correlations, multiple regression models, and hierarchical regression models were conducted in SPSS 24.0 and R Studio (Boston, MA) and the results reported in this chapter. The first section presents the sample description derived from frequencies, means, standard deviations, and ranges. The second section provides the results of univariate analyses used to better understand the study variables of interest and to verify that assumptions were met for each statistical test. The variables of interest include: BMI, hip/waist circumference ratio (HWR), cognitive reserve (i.e. years of education completed), perceived stress, loneliness, anxiety, depression, fatigue, self reported physical activity, sleep quality, daytime sleepiness, verbal learning performance, verbal fluency performance, executive functioning performance, serum IL-6 concentration, and serum TNF-α concentration. The third section presents multivariate analyses used for to address each aim, along with additional exploratory analyses.

SAMPLE DESCRIPTION

Demographic and treatment characteristics of both the 66 participants with complete data and the 75 participants (without cytokine data) in this study are displayed in Table 4.1. The sample with complete data (n=66) will be described here. The sample was on average years old 49 years of age (*SD* 8.77). The majority were white (93.4%),

Table 4.1

Demographic and Treatment Variables for Sample with Complete Data including Cytokines (n=66) and Incomplete data (N=75)

	Complete Data (n=66)			Incomplete Data (N=75)		
Characteristic	n (%)	Mean (SD)	Min, Max	n (%)	Mean (SD)	Min, Max
Age		49 (8.77)	27, 65		49.08 (9.04)	24, 65
Race						
White	62 (93.4%)			68 (90.7%)		
African American	1 (1.5%)			4 (5.3%)		
Asian	3 (4.5%)			3 (4.0%)		
Ethnicity						
Hispanic	3 (4.5%)			4 (5.3%)		
Non-Hispanic	63 (95.5%)			71 (94.7%)		
Years of Education		16.7 (2.16)	12, 22		16.6 (2.16)	12, 22
Highest Degree						
Highschool/Vocational	8 (12.1%)			11 (14.6%)		
Associates	5 (7.6%)			5 (6.7)		
Bachelors	30 (45.5%)			35 (46.7%)		
Graduate	23 (34.8%)			24 (32%)		
Maritial Status						
Married/Living with Sig.						
Other	46 (69.7%)			50 (66.7%)		
Divorced/Separated	6 (9.1%)			10 (13.3%)		
Never Married	14 (21.1%)			15 (20%)		
Have Children	42 (63.6%)			48 (64%)		
Employment Status						

Table 4.1 (continued)

Work full time/fulltime student	39 (59.1%)			48 (64%)		
Work part time	18 (27.3%)			18 (24%)		
Fulltime home-maker	3 (4.5%)			3 (4%)		
Unemployed	1 (1.5%)			4 (5.3%		
Retired	2 (3%)			2 (2.7%)		
Household Income (n=64, 2 missing)						
$0-50,000	7 (10.6%)			9 (12%)		
$50,000-99,999	22 (33.3%)			28 (37.3%)		
$100,000-149,000	16 (24.2%)			16 (21.3%)		
$150,000-199,999	10 (15.2%)			10 (13.3%)		
$200,00 or more	9 (13.6)			10 (13.3%)		
BC Type						
IDC	46 (69.7%)			50 (66.7%)		
DCIS	10 (15.2%)			14 (18.7%)		
ILC	5 (7.6%)			6 (8%)		
Multiple (IDC/DCIS/ILC)	5 (7.6%)			5 (6.7%)		
Stage						
1	12 (18.2%)			13 (17.3%)		
2	41 (62.1%)			46 (61.3%)		
3	13 (19.7%)			16 (21.3%)		
ER Recepter +	56 (84.8%)			63 (84%)		
HER 2 +	26 (39.4%)			28 (37.5%)		
Chemo Regimens						
Anthracyclines	37 (56.1%)			42 (56%)		
Non-Anthracyclines	29 (43.9%)			33 (44%)		
Months since Chemo		35.7 (27.12)	6.83, 120.84		37.00 (27.67)	6.83, 120.84
6mo-12mo	13 (19.7%)			16 (21.3%)		

Table 4.1 (continued)

1yr-2 yr	14 (21.1%)	14 (18.7%)
2yr- 4yr	23 (34.8%)	25 (33.3%)
4yr-6yr	10 (15.2%)	12 (16%)
6yr- 10yr	6 (9.1%)	8 (10.7%)
Hormonal Treatment (n=61)		
tamoxifen	40 (60.6%)	43 (68.25%)
Non-tamoxifen	21 (34.3%)	20 (31.75%)
Treatment Modalities		
Surgery	65 (98.5%)	74 (98.7%)
Radiation	40 (60.6%)	47 (62.7%)
Hormones	56 (84.8%	63 (84%)
Herceptin	26 (39.4%)	28 (37.3%
Menopausal Status		
Pre	10 (15.2%)	11 (14.7%)
Peri	9 (13.6%)	10 (13.3%)
Gone through	13 (19.7%)	15 (20%)
Chemical/surgical induced	34 (51.5%)	39 (52%)
Currently on Hormonal Therapy	44 (66.6%)	48 (64%)

Note. BC= Breast Cancer; IDC= Invasive Ductal Carcinoma; DCIS= Ductal Carcinoma In Situ; ILC= Invasive Lobular Carcinoma

non-Hispanic (95.5%) college educated (80.3%), married or living with a significant other (69.7%). Almost half were living on a household income of <$99,000 (43.9%) and the other half above $99,000 (53%).

The majority of the women had a history of stage II or III (81.8%) invasive ductal carcinoma breast cancer (69.7%) that was hormone receptor positive (84.8%). Almost all were treated with surgery (98.5%); the majority had radiation therapy (60.6%) in addition to anthracycline-based chemotherapy (56.1%) and some type of hormonal therapy (92.4%). Approximately 72% had gone through menopause already, either naturally or chemically/ surgically induced, and 66.6% were currently on hormonal therapy. On average, the women in the sample had completed chemotherapy three years prior (37 months ± 27.67 months)— approximately 75% were within four years of chemotherapy completion.

UNIVARIATE ANALYSES

The descriptive statistics and reliability for all the scales and subscales in the sample with complete data (n=66) are presented in Table 4.2 below (mean, standard deviation, median, minimum and maximum values, Shapiro-Wilk significance value, Skewness statistic, Kurtosis statistic, Chronbach's Alpha). The descriptive statistics and reliability for all the scales and subscales in the sample with incomplete data (N=75) are almost identical and are presented in Appendix M.

Individual Factors

BMI and HWR. On average the sample had a BMI of 27.36 (*SD* 5.46). BMI's ranged from 18.62 to 42.46 with a median of 25.79. According to the World Heath Organization, a healthy BMI is 18- 25, overweight ranges from 25-30, and those greater

Table 4.2
Study Variable Descriptive Statistics (n=66)

Measure	Mean (SD)	Min, Max	Median	Shapiro-Wilk◆	Skewness (std. error)	Kurtosis (std. error)	Cronbach's Alpha
BMI	27.36 (5.46)	18.62, 42.46	25.79	.001	0.87(0.30)	0.04 (0.58)	
HWR	0.82 (0.18)	0.62, 1.51	0.79	.000	2.83(0.38)	8.43 (0.58)	
Years Education	16.71 (2.16)	12, 22	16	.000	0.14 (0.30)	0.32 (0.58)	
PROMIS Anxiety	16.61 (7.88)	8, 40	16	.000	1.01 (0.30)	0.82 (0.58)	.96
PROMIS Depression	13.41 (6.21)	8, 32	11	.000	1.33 (0.30)	1.21 (0.58)	.94
PROMIS Fatigue	21.21 (8.05)	8, 39	20	.081	0.40 (0.30)	-0.49 (0.58)	.96
PSS	14.07 (8.03)	0, 31	14.5	.025	0.13 (0.30)	-0.83 (0.58)	.94
UCLA-R	37.93 (11.14)	20, 60	36	.000	0.25 (0.30)	-0.81 (0.58)	.95
IPAQ				.000			
Tot Active Min	975.29 (712.73)	0, 2400	752.50	.000	0.80 (0.30)	-0.54 (0.58)	
Tot Sit Min	3050.83 (1087.38)	540, 5130	2790	.023	0.29 (0.30)	-0.26 (0.58)	
PSQI Total	7.61 (4.35)	0, 17	7.0	.000	0.31 (0.30)	-0.77 (0.58)	.74
Sleep Quality	0.97 (0.70)	0, 3	1.0	.000	0.04 (0.30)	-0.91 (0.58)	
Latency	1.05 (1.16)	0, 3	1.0	.000	0.59 (0.30)	-1.18 (0.58)	
Duration	0.73 (0.87)	0, 3	1.0	.000	1.15 (0.30)	0.75 (0.58)	
Efficiency	1.03 (1.26)	0, 3	0.0	.000	0.70 (0.30)	-1.27 (0.58)	
Disturbance	1.61 (0.60)	0, 3	2.0	.000	-0.42 (0.30)	-0.02 (0.58)	
Sleepaid	1.24 (1.38)	0, 3	0	.000	0.34 (0.30)	-1.79 (0.58)	
Daytime Dysfunction	0.98 (0.73)	0, 3	1.0	.000	0.27 (0.30)	-0.39 (0.58)	
ESS	6.98 (4.59)	0, 18	6	.000	0.64 (0.30)	-0.66 (0.58)	.84
IL-6 (pg/ml)	2.25 (1.80)	.05, 7.62	1.95	.000	1.36 (0.30)	1.56 (0.58)	
TNF-α (pg/ml)	5.91 (1.40)	2.98, 10.09	5.98	.121	0.51 (0.30)	0.40 (0.58)	
IL-6*TNF-α (pg/ml)	13.72 (12.43)	0.32, 64.92	10.20	.000	1.74 (0.30)	3.74 (0.58)	
log 10 IL-6	0.19 (0.44)	-1.30, 0.88	0.29	.001	-1.17 (0.30)	2.1 (0.58)	
log 10 TNF-α	0.76 (0.10)	0.47, 1.00	0.77	.510	-0.18 (0.30)	0.02 (0.58)	

Table 4.2 (continued)

log 10 IL-6* log 10 TNF-α	0.15 (0.35)	-1.1, 0.82	0.21	.003	-1.1 (0.30)	2.1 (0.58)	
FACT- Cog Total^	94.99 (34.87)	19, 147	95.5	.013	-0.43 (0.30)	-0.70 (0.58)	.98
PCI	47.59 (20.93)	3, 79	50.5	.010	-0.35 (0.30)	-0.89 (0.58)	.97
Impact on QOL	10.79 (5.03)	0, 16	12	.000	-0.89 (0.30)	-0.32 (0.58)	.95
Others	14.06 (3.19)	3, 16	16	.000	-1.95 (0.30)	3.12 (0.58)	.90
PCA	22.55 (8.77)	4, 36	221	.050	-0.15 (0.30)	-0.83 (0.58)	.93
HVLT Immediate Raw	29.80 (3.60)	21, 36	30	.019	-0.51 (0.30)	-0.50 (0.58)	-
HVLT Delayed Raw	10.61 (1.47)	6, 12	11	.000	-1.10 (0.30)	0.84 (0.58)	-
COWAT Raw	40.18 (11.29)	16, 71	39.5	.404	0.41 (0.30)	0.31 (0.58)	-
Trails A Raw	26.36 (9.17)	11.5, 54	24.3	.000	1.16 (0.30)	0.77 (0.58)	
Trails B Raw	56.72 (23.03)	26.5, 179.5	50.83	.000	2.80 (0.30)	11.89 (0.58)	

Note. BMI= Body Mass Index; HWR= Hip to Waist Ratio; PSS= Perceived Stress Scale; UCLA-R= UCLA Loneliness Scale Revised version 3; IPAQ= International Physical Activity Questionnaire; PSQI= Pittsburgh Sleep Quality Index; ESS= Epworth Sleepiness Scale; IL-6= Interleukin 6; TNF- α = Tumor Necrosis Factor- α; FACT-Cog Version 3= Functional Assessment of Cancer Treatment- Cognition Version 3; PCI= Perceived Cognitive Impairments Subscale; PCA= Perceived Cognitive Abilities Subscale; Others= Comments from Others Subscale, Impact= Impact on Quality of Life; HVLT=Hopkins Verbal Learning Test; COWAT= Controlled Oral Word Association Test; TMT= Trail Making Test

◆ For the Shapiro-Wilk Test, the null hypothesis of this test is that the population is normally distributed. Thus, if the p-value is less than the chosen alpha level then the null hypothesis is rejected and there is evidence that the data tested are not from a normally distributed population

^ Fact Cog Total: lower scores indicate lower overall functioning; PCI: lower scores indicate worse cognitive impairments; Impact on QOL: Higher scores, better QOL lower scores worse QOL; Comments from Others: lower scores, worse comments from others ; PCA: Higher scores, better abilities, lower scores worse perceived abilities

than 30 are considered obese (http://www.who.int/mediacentre/factsheets/fs311/en/). The average HWR in the study was 0.82 (*SD* 0.18), and the median HWR was 0.79. A HWR of 0.80 or greater is considered a marker of central obesity ("Waist circumference and waist–hip ratio: report of a WHO expert consultation", 2008). Although the Shapiro-Wilk test for both of these measures was significant, the skewness and kurtosis absolute values are less than 1.0, and the mean and median similar, suggesting normal distribution.

Cognitive Reserve (Years education). On average the participants in this study had completed 16.71 years of formal education (*SD* 2.16), which equates to completion of high school and a four-year bachelor's degree. The median for years of education was also 16. Although the Shapiro-Wilk test this measure was significant, the skewness and kurtosis absolute values are less than 1.0, and the mean and median similar, suggesting normal distribution.

Psychosocial Factors

Emotional Distress and Fatigue. Three of the NIH PROMIS scales were used to assess aspects of emotional distress and fatigue— PROMIS Item Bank v1.0 – Emotional Distress – Anxiety – Short Form 8a, PROMIS Item Bank v1.0 – Emotional Distress – Depression – Short Form 8a, and the PROMIS Item Bank v1.0 – Emotional Distress – Fatigue – Short Form 8a. The average score on the PROMIS Anxiety was 16.61 (SD 7.88) and the median was also 16. The highest possible score on this scale is 40, and higher scores indicate more anxiety. For the PROMIS Depression, participants averaged a score of 13.41 (SD 6.21), with a median score of 11. The highest possible score on this scale is 40, and higher scores indicate more depressive symptoms. The highest average was found on the PROMIS Fatigue with a mean of 21.21 (SD 8.05) and a median of 20. The highest possible score on this scale is 40, and higher scores indicate more fatigue.

The Shapiro-Wilk tests for all these scales were all significant (except for the PROMIS Fatigue); however, the skewness and kurtosis absolute values were less than 1.33, suggesting normal distribution. Furthermore, the Chronbach's alphas ranged from 0.94-0.96 for the PROMIS scales.

Perceived Stress. On average, participants scored 14.07 (*SD* 8.03) on the PSS. Total scores ranged from 0 to 31, with a median of 14.5. The highest possible score on this scale is 40, higher scores indicate higher perceived stress. The Shapiro-Wilk test for this measure was non-significant and the skewness and kurtosis absolute values both less than 1.0 suggesting normal distribution. The Chronbach's alpha in this study was 0.94.

Social Isolation. The average score on the UCLA-R was 37.93 (*SD* 11.14) and a median of 36. Total scores ranged from 20-60. The maximum possible score on this scale is 80, indicating greater degrees of perceived social isolation. The Shapiro-Wilk test this measure was significant; however, the skewness and kurtosis absolute values both less than 1.0 suggesting normal distribution. The Chronbach's alpha in this study was 0.95.

Behavioral Factors

Physical Activity. Two subscales of the IPAQ were evaluated: total minutes spent doing physical activity (Total Active Min) and total minutes spent sitting (Total Sit Min). Originally, the distributions of these two variables were not normal. The mean for Total Active Min was 1,095 min (*SD* 1068) median 752, was skewed (2.31) with a large value of kurtosis (6.55). Similarly, the mean for Total Sit Min was 3,138 (*SD* 1320, median 2790) was skewed (1.27) with a large kurtosis value (2.99). Therefore, the outliers were examined for each subscale. For the Total Active Min scale, five outliers were identified and the four outliers with the highest values were adjusted to the value of the lowest of all five outliers— 2400 min. The same process was used to identify the

outliers for Total Min Sit subscale, and the top four outliers were changed to the lowest value of all five outliers—5130 min. After these adjustments were made, the distributions for these two subscales were normal. For the Total Active Min scale, the mean was of 975.29 min (*SD* 712.73), median 752.5 and scores ranged from 0 to 2400. The skewness statistic was reduced to 0.80 and kurtosis to -0.5. For Total Sit Min subscale, the mean was 3050.83 (*SD* 1087.38), median 2790, with scores ranging from 540-5130. The skewness value was reduced to 0.29 and kurtosis to -0.26. These two scales were used in the multivariate analyses. When frequencies were evaluated, 46% of participants reported engaging in 500-1500 min of activity in the previous week, and over 60% reported sitting between 2000-4000 min the previous week. The frequency distribution for IPAQ Act Min and IPAQ Min Sit are graphically depicted in the bar graphs in Appendix N.

Sleep Quality. The PSQI has seven components or subscales that are summed to form a total sleep quality score. Higher scores indicate poorer sleep quality. The participants in this study scored on average 7.61 (*SD* 4.35) on the total scale, with a minimum of 0 and a maximum of 17 and the median score 7. The clinical cut off for the PDQI is six. Those who score six or greater on the PSQI are considered poor sleepers. The average score on PSQI in this sample was comparable to other studies conducted with breast cancer survivors (Berger et al., 2012; Enderlin et al., 2011; Mustian et al., 2012; Otte et al., 2010). The Shapiro-Wilk test for the PDQI total and the subscales the Shapiro-Wilk tests were all significant. The skewness and kurtosis absolute values are less than 1.79 for all the subscales suggesting close to normal distribution. The reliability of the PSQI was satisfactory, at 0.74. The ESS, a measure of daytime sleepiness was also used to assess sleep quality. Score on this measure ranged from 0 to 18, with an average score of 6.98 (*SD* 4.59) and a median of 6. This average is similar to another study conducted with breast cancer survivors (Enderlin et al., 2011). The Chronbach's alpha

was 0.84. Both PSQI total score and ESS were used in multivariate analyses depending on the model being tested.

Biological Factors

Cytokines. Human high sensitivity T cell magnetic bead panel (multiplex) assays were used for the simultaneous quantification of IL-6 and TNF-α in participants' serum following the manufacturer's procedures (EMD Millipore). The samples were run in duplicates, and in the event that an intra assay precision (CV%) was greater than 15%, the sample was re-run. According to the FDA, intra assay precision CV percent's up to 15% are acceptable. The quality controls for both IL-6 and TNF-α were within the expected ranges. The standards for both analytes were used to make the standard curve of MFI to analyte concentration (Figures 4.1 and 4.2). The R^2 for IL-6 was 1.0 and for TNF-α it was 1.0. A R^2 close to 1.0 is desired.

The levels (pg/ml) of IL-6 ranged from 0.05 to 99.79 pg/ml. The participant with 99.79 pg/ml was an outlier, the next highest value was only 7.62 pg/ml. To preserve the sample size, rather than dropping the participant with the 99.79 pg/ml value for IL-6, the value for this participant was changed to 7.62 pg/ml the next most extreme score (Munroe, 2005). With this adjustment, the average concentration of IL-6 was 2.25 pg/ml (*SD* 1.80) with a median of 1.95 pg/ml. The Shapiro-Wilk test was significant, and the absolute skewness and kurtosis values less 1.56 or less, suggesting abnormal distribution. The levels (pg/ml) of TNF-α ranged from 2.98 to 10.09 pg/ml, with an average of 5.91 pg/ml (SD 1.40) and a median of 5.98. The Shapiro-Wilk test was non-significant, and the absolute skewness and kurtosis values less than 1.0, suggesting normal distribution. Since IL-6 has been described as both pro-inflammatory and anti-inflammatory, it's possible that the interaction between for IL-6 and TNF-α could provide a better understanding of these cytokines in the context of the biobehavioral model. Therefore, an

Figure 4.1 Standard curve of MFI to IL-6 Concentration

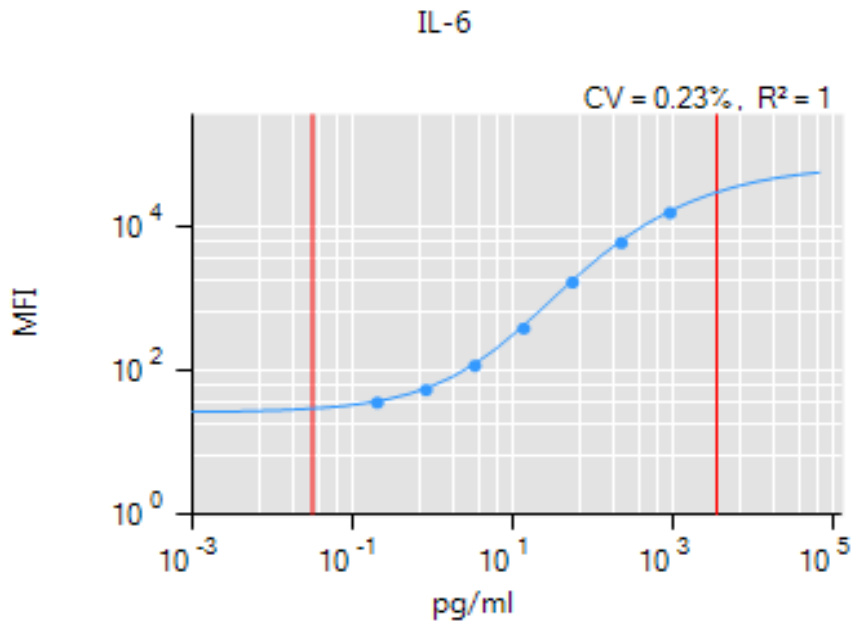

Figure 4.1. The standard curve of MFI to concentration of IL-6 calculated from the standards in the Multiplex Kit. An R^2 close to 1 is desired.

Figure 4.2 Standard curve of MFI to TNF-α Concentration

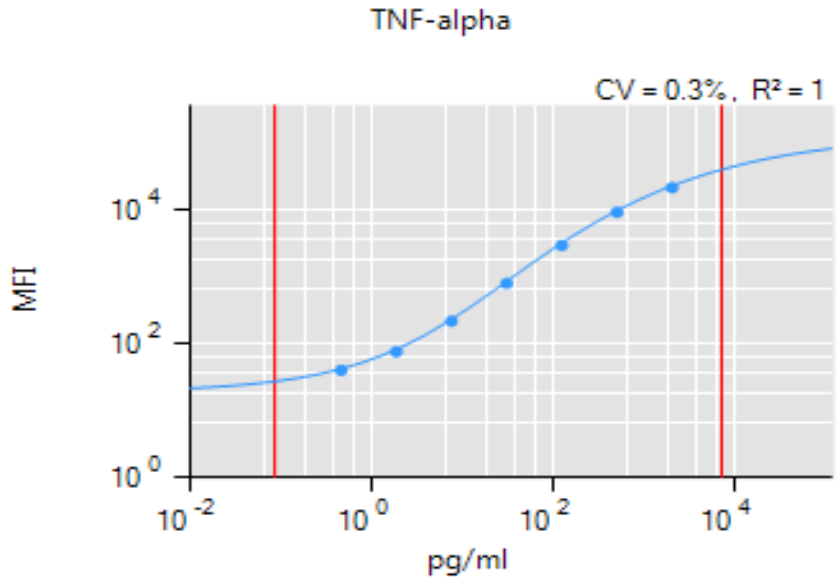

Figure 4.2. The standard curve of MFI to concentration of TNF-α calculated from the standards in the Multiplex Kit. An R^2 close to 1 is desired

interaction variable for IL-6 and TNF-α (IL-6*TNF-α) was also created. The levels (pg/ml) of IL-6*TNF-α interaction ranged from 0.32- 64.92 pg/ml, with an average of 13.72 pg/ml (SD 12.43) and a median of 10.20. The Shapiro-Wilk test was significant, and the absolute skewness and kurtosis values less than 1.74-3.74, suggesting non-normal distribution, therefore, both IL-6 and TNF-α were transformed using the $\log_{10}$ transformation, and a new interaction term was created by multiplying the $\log_{10}$ of IL-6 and the $\log_{10}$ of TNF-α.

Cognitive Outcomes

Perceived Cognitive Function. The FACT-Cog was used to evaluate perceived cognitive function in this sample. This instrument has a total score and four subscales. Higher scores indicate better cognitive functioning. For the total scale score, participants ranged from 19 to 147, and averaged 94.99 (*SD* 34.87), with a median of 95.5. For this instrument, lower scores indicate poorer functioning, or worse quality of life. On the Perceived Cognitive Impairments subscale (PCI), the average score was 47.59 (*SD* 20.93) but scores ranged from 3 to 79. On the Impact on Quality of Life Scale, the average score was 10.79 (*SD* 5.03), and for the Comments from Others subscale the mean 14.06 (*SD* 3.19). Finally for the Perceived Cognitive Abilities Subscale (PCA), scores ranged from 4 to 36, with the average score being 22.55 (*SD* 8.77). The Shapiro-Wilk tests for all these scales were significant (except for the total scale); however, the skewness and kurtosis absolute values were less than 1.0 (except on the Comments from Others subscales), suggesting close to normal distribution. Furthermore, the Chronbach's alphas in this study ranged from 0.90 to 0.98 on the FACT-Cog total and subscales. The FACT-Cog Total, PCA, and the PCI scores were used as outcome variables in multivariate analyses.

Cognitive Performance. The brief NP battery administered to each participant consisted of four tests evaluating short and long term verbal memory (HVLT-Immediate,

HVLT-Delayed), verbal fluency (COWAT), attention (Trails A) and executive functioning (Trails B). First, all NP measures were age and education-adjusted based on the established norms, in order to profile and describe the sample. These standardized scores are illustrated in boxplots below in Figures 4.3 - 4.5. On both the HVLT-Immediate and Delayed recall, participants scored between 0 and 1 standard deviation above the mean. Adjusted scores on the COWAT were just above average— mean around 60%. Scores on the Trails A and Trails B were average.

Within the field of CRCI, mild cognitive impairment has been classified as -1.5 SD below the age and education adjusted mean. For descriptive purposes, standardized scores for each of the NP normed scores were dichotomized into impaired or not impaired. For HVLT-I, 4.5% of the sample were considered impaired; for HVLT-D, 4.5% were considered impaired; for COWA, 6.1% were considered impaired; for Trails A, 9.1% were considered impaired; and for Trails B, 7.6% were considered impaired. Across all tested domains, nine participants (13.6%) displayed mild cognitive impairment in one cognitive domain; one participant (1.5%) displayed mild cognitive impairment in two cognitive domains; two participants (3%) displayed mild cognitive impairment in three cognitive domains; and one participant (1.5%) displayed mild cognitive impairment in four cognitive domains. Approximately 20% of the sample displayed mild cognitive impairment in at least one cognitive domain.

Raw test scores were used in all univariate and multivariate analyses. All descriptive data for the NP scores can be found above in Table 4.2. Both the Trails A and Trails B were skewed, the Trails B with more extreme skewness so these two raw scores were

Figure 4.3 Box plots of Standardized HVLT Scores (Immediate and Delayed)

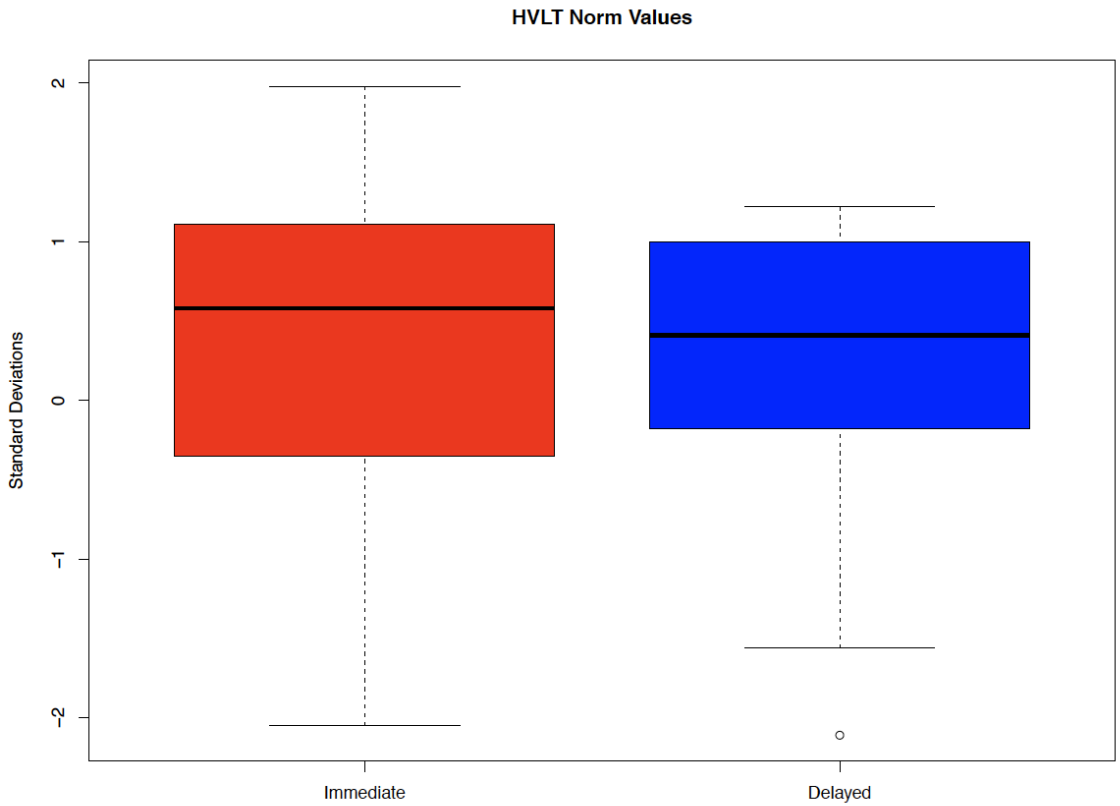

Figure 4.3. Boxplot distribution of the HVLT-Immediate (red) and Delayed (blue) scores after age and education adjustments, presented in standard deviation.

Figure 4.4 Box plots of Standardized COWAT Scores

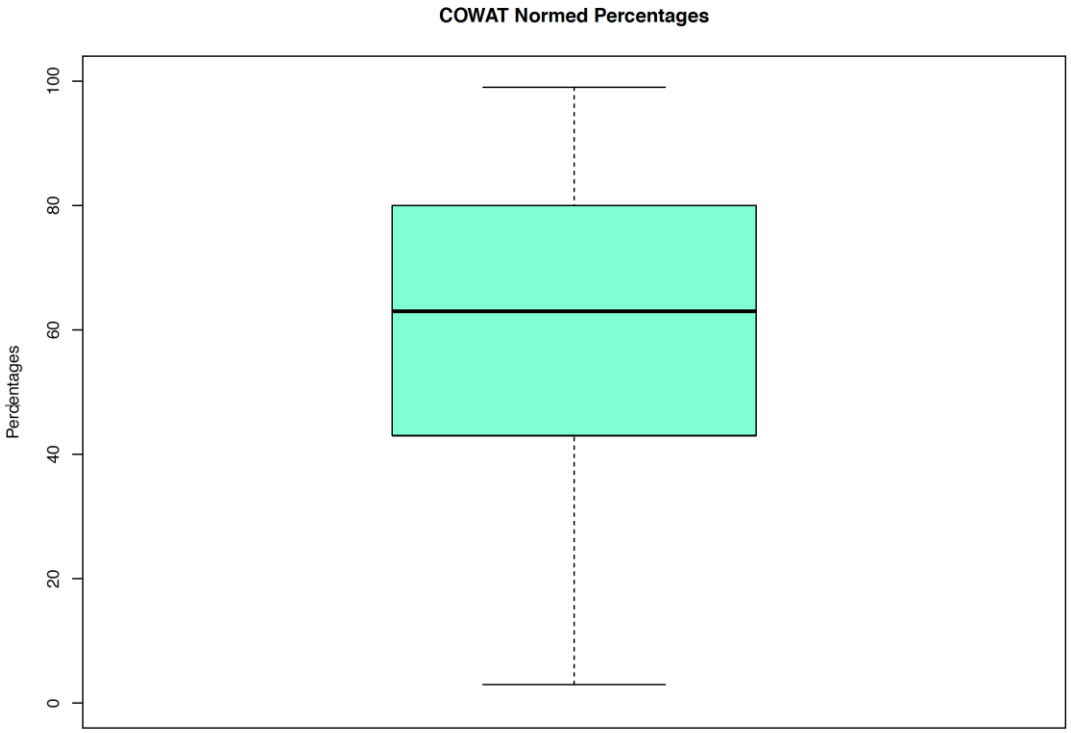

Figure 4.4 Box plots distribution of standardized (age and education adjusted) COWAT scores, displayed as percentiles.

Figure 4.5 Box plots of Trails A and B Adjusted Scores

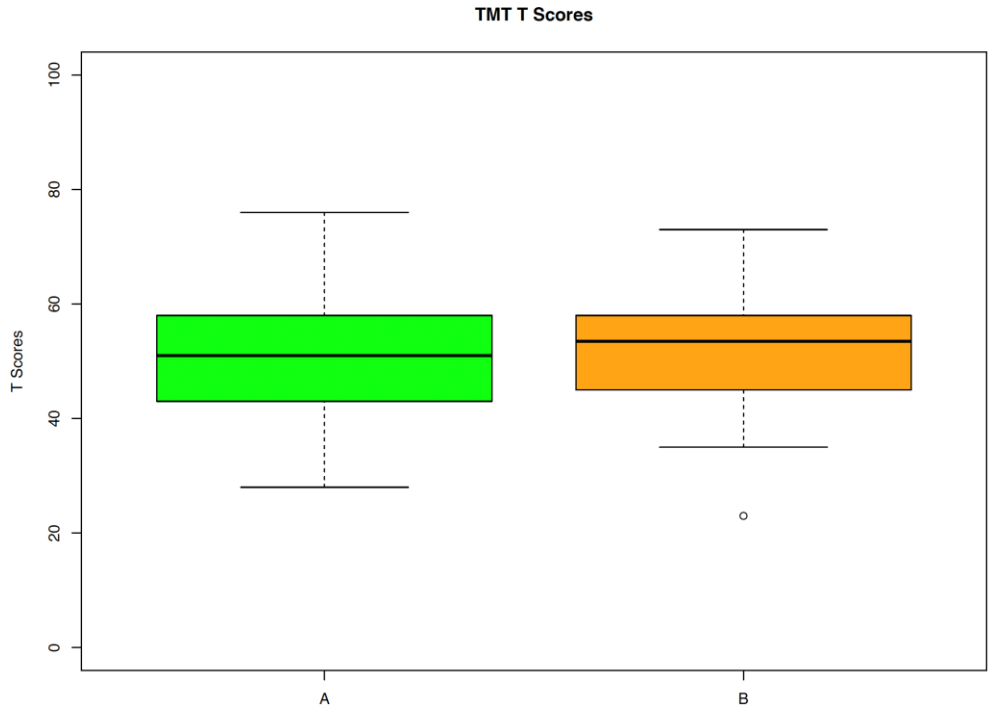

Figure 4.5 Box plots distributions of Trails A (green) and B (orange) t scores, adjusted for age, education, and race.

transformed according to Munroe (2005). The square root transformation was used for Trails A and the log 10 used for Trails B.

Outliers and Basic Assumptions

The Shapiro-Wilk statistic was significant for all of the scales except for the HVLT-Immediate, COWAT, PROMIS Fatigue, IPAQ Total Sit Min, TNF-α, and FACT-Cog Total, suggesting that vast majority of the data collected in this sample were not normally distributed. This test was interpreted with caution because sample size can impact the significance of the Shapiro-Wilk test (Ghasemi & Zahediasl, 2012), thus other methods of evaluating distribution were employed. When evaluating normality based on skewness, with a criteria for skewness being an absolute value greater than 1.5, skewed distributions were found for the following measures: HWR (2.83); IL-6 and TNF-α interaction term (1.74); FACT-Cog Comments from others subscale (-1.95); and Trails B Raw score (2.80).

Several outliers were identified during univariate analyses on the following measures: 1) HVLT-Delayed; 2) COWAT; 3) Trails A; 4) Trails B; 5) FACT-Cog Comments from Others Subscale; 6) PROMIS Depression; 7) IPAQ Tot Active Min (these outliers were changed to 2400 min); 8) IPAQ Sit Min (these outliers were changed to 5130 min); 9) HWR; 10) Years of Education; 11) IL-6; 12) TNF- α; and 13) IL-6*TNF- α interaction. Each case was located in the dataset and compared against original survey and test data to ensure that the correct data were entered. Furthermore, any notes that were made in the participant file were reviewed to identify any contextual reasoning behind the outlying value. See "Predictor Variables and Dependent Variables Outliers and Assumptions Table" in Appendix O for a summary of all results of the study variable outliers and assumption checks.

The only data that were transformed were the cytokine data (log_{10} transformations), Trails A raw scores (square root transformation), and Trails B raw scores (log_{10} transformation). The other data that were skewed to lesser degrees were not transformed because transforming data can make interpretation difficult (Munroe, 2005).

MULTIVARIATE ANALYSES

Correlations Among Variables

Zero order correlations were examined to identify high levels of shared variance among the predictor variables (>.85) and to facilitate linearity assessment. These correlations are displayed in Tables 4.3-4.5. Pearson's correlations were used for continuous variables, and Kendall's Tau correlations were used for ordinal and nominal associations.

First, the correlations were examined between the individual factors of interest (Age, BMI, HWR, Anthracycline Chemotherapy, Tamoxifen Treatment, Race, Ethnicity, breast cancer stage, and months since end of chemotherapy), predictor variables (PROMIS Anxiety, PROMIS Depressive Symptoms, PROMIS Fatigue, PSQI, IPAQ, ESS, PSS, UCLA-R), and log_{10} transformed cytokine concentrations (IL-6, TNF-α, IL-6*TNF-α) and are displayed in Table 4.3. Only one small-positive significant correlation was found between BMI and log_{10}TNF-α (r = .26, p < .05) suggesting that as BMI increases so does the log_{10} value of TNF-α. All remaining correlations were small and non-significant.

Next, the correlations between the log_{10} transformed cytokine concentrations (IL-6, TNF-α, IL-6*TNF-α) and the cognitive outcomes (FACT-COG Total, PCI subscale, PCA subscale, HVLT-I Raw Scores, HVLT-D Raw Scores, COWAT Total Raw Scores, Trails A transformed scores, and Trails B transformed scores) were examined and are

Table 4.3

Correlations between Individual Factors, Predictor Variables, and log10 Cytokine Concentrations (n=66)

	log_{10}IL-6	log_{10}TNF-α	log_{10}IL-6* log_{10}TNF-α
Age	.09	-.10	.07
BMI	.00	.26*	.03
HWR	-.10	.16	-.10
Anthracycline Chemo	-.19	.18	-.19
Tamoxifen Treatment■	-.04	-.08	-.05
Ethnicity✡	.06	.08	.04
Race	.13	.02	.12
Breast Cancer Stage	-.14	.13	-.13
Months Since end of Chemo	-.01	-.13	-.03
PROMIS Anxiety	.07	-.10	.06
PROMIS Depressive	.10	-.03	.10
PROMIS Fatigue	.02	-.08	.03
PSQI Total	.02	-.16	-.01
IPAQ Tot Min Sit	-.06	.14	-.05
IPAQ Tot Active Min	.22#	-.01	.20
UCLA-R	-.04	-.08	-.03
PSS	-.12	-.15	-.13
ESS	-.13	-.11	-.12

Note. Significance not corrected for multiple comparisons for exploratory descriptive purposes.
Pearson's *R* used for interval level variables, all categorical variables were dummy coded and Kendall's tau correlations were used.
=0=non anthracycline, 1= anthracycline
■ = 0=no tamoxifen, 1= tamoxifen
✡= 0=Non-Hispanic; 1= Hispanic
** p<.05,# p<0.10*

displayed in Table 4.4. No significant relationships were identified between these variables.

Finally, correlations were examined between the individual factors, predictor variables, and the cognitive outcomes—both the perceived cognitive function (FACT-Cog, PCI, PCA) and cognitive performance (HVLT-I, HVLT-D, COWAT, Trails A transformed, and Trails B transformed). Since these data were available for all 75 participants, the correlations were evaluated using this larger sample and displayed in Table 4.5. Among the individual factors and perceived cognitive function, small negative relationships were found between BMI and FACT-Cog Total and PCA (*r's*= -.23 to -.25, *p's* < .05) and small negative relationships approached significance between FACT-Cog scores and ethnicity (*r's*= - .16 to -.17, *p's* < .10). Moderate to large negative significant relationships were found between PROMIS Anxiety, Depression, and Fatigue and the FACT-Cog total and subscales (*r's*= -.50to -.66, *p's* < .001). The predictor variables were measured with the PSQI, IPAQ Min Sit, IPAQ Act Min, ESS, PSS, and UCLA-R scales. Among the predictor variables, moderate to large negative relationships were found between PSQI and the FACT-Cog (*r's*= -.43 to -.49, *p's*< .001); the UCLA-R and the FACT-Cog (*r's*= -.46 to -.56, *p's* < .001); PSS and FACT-Cog (*r's*= -.60 to -.71, *p's* < .001); and the ESS and FACT-Cog (*r's*= -.35 to -.42, *p's* <.001).

Among the individual factors and cognitive performance, age was significantly related to HVLT-D and transformed Trails A & B (absolute value of *r's* = .26 to .42, *p's* < .05). Small positive relationships were found between years of education and HVLT-D (*r*= .26, *p*< .05) and COWAT scores (*r*= .28, *p* < .05). Treatment with anthracycline-based chemotherapy was significantly related to COWAT scores (*r*= .20, *p* < .05). Breast cancer stage was significantly related to transformed Trails B scores (*r*= -.19, *p* < .05). Ethnicity was significantly related to COWAT scores(*r*=-.20, *p* <.05). Among the

Table 4.4

Pearson's Correlations between Cytokines and Cognitive Measures (n=66)

	log_{10}IL-6	log_{10}TNF-α	log_{10}IL-6* log_{10}TNF-α
FACT-Cog	.04	.13	.04
PCI	.06	.15	.05
PCA	.06	.10	.05
HVLT-Immediate	-.15	.02	-.16
HVLT Delayed	-.04	.02	-.06
COWAT	-.17	-.06	-.14
TMT A[a]	.09	.02	.08
TMT B[b]	.11	.14	.12

Note. a= Transformed data used (sq rt transformation); b= Transformed data used (log 10 transformation)

Table. 4.5

Correlations between Individual Factors, Predictor Variables, and Cognitive Outcomes (N=75)

	FACT-Cog	PCI	PCA	HVLT-I	HVLT-D	COWAT	TMT A[a]	TMT B[b]
Age	.06	.03	.07	-.10	-.26*	-.07	.42***	.36**
BMI	-.23*	-.25*	-.21[#]	.05	.00	-.15	.15	.10
HWR	.06	.06	.10	.10	.17	.12	-.14	-.11
Years Education	.07	.06	.10	.22[#]	.26*	.28*	-.08	-.07
Anthracycline Chemo	.06	.07	.05	-.05	.02	.20*	-.17[#]	-.10
Tamoxifen Treatment■	-.14	-.15	-.15	.10	.07	-.04	.06	.09
Ethnicity☓	-.17[#]	-.17[#]	-.16[#]	-.17[#]	-.05	-.20*	-.05	-.01
Race	-.10	-.09	.04	.09	.18[#]	.09	-.13	-.16[#]
Breast Cancer Stage	-.03	-.01	-.04	-.15	-.11	-0.14	-.01	-.14
Months Since end of Chemo	-.09	-.10	-.02	.05	-.15	-.09	.13	.08
PROMIS Anxiety	-.65***	-.62***	-.52***	-.06	-.09	-.05	.04	.03
PROMIS Depressive	-.61***	-.57***	-.50***	-.10	-.15	-.10	.09	.08
PROMIS Fatigue	-.66***	-.61***	-.59***	-.02	-.09	-.10	-.03	.09
PSQI Total	-.49***	-.46***	-.43***	-.01	-.22[#]	-.05	.09	.10
IPAQ Sit Min	-.12	-.17	-.09	.01	.22[#]	.08	.05	-.01
IPAQ Active Min	.01	.01	.04	-.09	-.17	-.16	.19	.25*

Table 4.5 (continued)

UCLA-R	-.56***	-.55***	-.46***	.06	-.04	-.07	.03	-.09
PSS	-.71***	-.68***	-.60***	-.10	-.07	-.13	.14	.09
ESS	-.40***	-.42***	-.35***	.17	.23*	-.14	-.17	-.12
FACT-Cog	1.0	.98***	.89***	.04	.09	.15	-.15	-.06

Note. Significance not corrected for multiple comparisons for exploratory descriptive purposes.

**** p<.001,** p <.01, * p<.05, # p<.01*

Pearson's *R* used for interval level variables, all categorical variables were dummy coded and Kendall's tau correlations were used.

=0=non anthracycline, 1= anthracycline

■ = 0=no tamoxifen, 1= tamoxifen

⁜= 0=Non-Hispanic; 1= Hispanic

a= Transformed data used (sq rt transformation)

b= Transformed data used (log 10 transformation)

PCI=FACT-Cog Perceived Cognitive Impairments Subscale, PCA= FACT-Cog Perceived Cognitive Abilities Subscale

predictor variables, measured with the PSQI, IPAQ Min Sit, IPAQ Act Min, ESS, PSS, and UCLA-R scales, small relationships approached significance between HVLT-D and PSQI (r= -.22, p < .10), ESS Scores (r= .23, p < .05), and IPAQ Min Sit (r= .22, p < .10). IPAQ Act Min was significantly related to Trails B scores (r= .25, p < .05). No significant relationships were found between the psychosocial variables (stress, perceived social isolation, anxiety, fatigue, depression) and the cognitive performance variables. Among the perceived cognitive function and cognitive performance variables, no significant relationships were found.

Regression analyses

Statistical Testing Assumptions

Normality, independence, linearity, and homoscedasticity assumptions for ordinary least squares regression were checked to ensure the validity, or probability of rejecting the null hypothesis was not higher than the chosen significance level, and power of this statistical analyses.

Normality was already assessed in the univariate analyses presented above. According to Hayes (2013), this assumption is one of the least important in regression analyses and simulation statistical research suggests that only severe violations of this assumption can affect the validity of statistical inference. Hayes also explains that when modeling non-normal variables using OLS regression, the errors in estimation tend to be not normal as well. The Shapiro-Wilk test was used to statistically analyze normality of the variables. Ghasemi & Zahediasl (2012) explain that even small deviations from normality will result in significant Shapiro-Wilk tests in larger samples (greater than 30-40), which explains why almost all of Shapiro-Wilk tests were significant in this study. Another assumption of OLS regression is that the errors in estimation are statistically

independent. The PI verified that the assumption of independence was met by her knowledge of participants enrolled in the study.

Linearity. Linear regression is largely based on linear associations between variables. These associations were first explored and reported in the "Correlations Among Variables" section above. Scatter plots (Y is plotted as a function of X) were examined first between the predictor variables (PROMIS scales, IPAQ Tot Min Sit, IPAQ Tot Act Min, PSQI Total, UCLA-R, PSS, ESS) and $\log_{10}$ transformed cytokines. A line of best fit was added to each scatterplot to determine nature of each relationship. The scatterplots revealed that relationships between predictor variables (psychosocial and behavioral factors) and cytokines were very small linear or non-linear. Nonlinear functions (i.e. quadratic, cubic) were evaluated to fit the data points in each scatterplot. It was determined that cubic functions fit these data best; therefore, the linear assumption was violated. The values for both Linear and Cubic R^2 lines of fit for each scatter plot are displayed in Table 4.6. The cubic regression models provided a better fit to the data.

Next, scatter plots were examined between the $\log_{10}$ transformed cytokines and the cognitive outcomes (FACT-Cog Total, PCI, PCA, HVLT-I, HVLT-D, COWAT, Trails A, Trails B). A line of best fit was added to each scatterplot to determine nature of each relationship. The scatterplots revealed that relationships between the cytokines and cognitive outcomes were very small linear or non-linear. Nonlinear functions (i.e. quadratic, cubic) were evaluated to fit the data points in each scatterplot. It was determined that cubic functions these data best, therefore, the linear assumption was violated. Both Linear and Cubic R^2 values for these scatter plots are displayed in Table 4.7.

Finally, scatter plots were examined between the predictor variables (IPAQ Sitting, IPAQ Active, PSQI Total, UCLA-R, PSS) and Cognitive Outcomes (NP

Table 4.6

R^2 values for Scatterplot Lines of Best fit between Individual Factors, Predictors Variables, and Cytokines (n=66)

	log_{10}IL-6	log_{10}TNF- α	log_{10}IL-6* log_{10}TNF-α
PROMIS Anxiety	R^2 Linear = .005	R^2 Linear = .009	R^2 Linear = .003
	R^2 Cubic = .011	R^2 Cubic = .013	R^2 Cubic = .008
PROMIS Depressive	R^2 Linear = .010	R^2 Linear = .001	R^2 Linear = .010
	R^2 Cubic = .011	R^2 Cubic = .001	R^2 Cubic = .011
PROMIS Fatigue	R^2 Linear = .000	R^2 Linear = .006	R^2 Linear = .001
	R^2 Cubic = .042	R^2 Cubic = .059	R^2 Cubic = .040
PSQI Total	R^2 Linear = .001	R^2 Linear = .025	R^2 Linear = .000
	R^2 Cubic = .006	R^2 Cubic = .039	R^2 Cubic = .008
IPAQ Tot Min Sit	R^2 Linear = .003	R^2 Linear = .020	R^2 Linear = .002
	R^2 Cubic = .027	R^2 Cubic = .114	R^2 Cubic = .026
IPAQ Tot Min Act	R^2 Linear = .045	R^2 Linear = .000	R^2 Linear = .041
	R^2 Cubic = .096	R^2 Cubic = .015	R^2 Cubic = .083
UCLA-R	R^2 Linear = .001	R^2 Linear = .007	R^2 Linear = .001
	R^2 Cubic = .036	R^2 Cubic = .018	R^2 Cubic = .040
PSS	R^2 Linear = .014	R^2 Linear = .024	R^2 Linear = .016
	R^2 Cubic = .050	R^2 Cubic = .048	R^2 Cubic = .048
ESS	R^2 Linear = .017	R^2 Linear = .012	R^2 Linear = .011
	R^2 Cubic = .149	R^2 Cubic = .032	R^2 Cubic = .115

Note. Line of best fit added to each scatterplot to determine nature of relationship with highest R^2. Cubic $R^2 \geq$ Quadratic R^2 in all the scatterplots; therefore only Linear and Cubic R^2 included in table.

Table 4.7

R^2 values for Scatterplot Line of Best fit Cytokines (X axis) and Cognitive Measures (Y axis) (n=66)

	log_{10}IL-6	log_{10}TNF-α	log_{10}IL-6* log_{10}TNF-α
	R^2 Linear = .022	R^2 Linear = .0003	R^2 Linear = .025
HVLT-Immediate	R^2 Cubic = .045	R^2 Cubic = .031	R^2 Cubic = .034
	R^2 Linear = .002	R^2 Linear = .0005	R^2 Linear = .004
HVLT Delayed	R^2 Cubic = .040	R^2 Cubic = .113	R^2 Cubic = .020
	R^2 Linear = .013	R^2 Linear = .003	R^2 Linear = .020
COWAT	R^2 Cubic = .022	R^2 Cubic = .063	R^2 Cubic = .031
	R^2 Linear = .008	R^2 Linear = .0004	R^2 Linear = .007
Trails A[a]	R^2 Cubic = .025	R^2 Cubic = .003	R^2 Cubic = .032
	R^2 Linear = .013	R^2 Linear = .020	R^2 Linear = .013
Trails B[b]	R^2 Cubic = .023	R^2 Cubic = .028	R^2 Cubic = .045
	R^2 Linear = .002	R^2 Linear = .017	R^2 Linear = .001
FACT- Cog Total	R^2 Cubic = .005	R^2 Cubic = .059	R^2 Cubic = .003
	R^2 Linear = .003	R^2 Linear = .023	R^2 Linear = .003
PCI	R^2 Cubic = .006	R^2 Cubic = .075	R^2 Cubic = .004
	R^2 Linear = .003	R^2 Linear = .009	R^2 Linear = .002
PCA	R^2 Cubic = .004	R^2 Cubic = .045	R^2 Cubic = .003

Note. Line of best fit added to each scatterplot to determine nature of relationship with highest R^2. Cubic $R^2 \geq$ Quadratic R^2 in all the scatterplots; therefore only Linear and Cubic R^2 included in table. In these scatterplots, cytokines were on the X axis, and cognitive measures on the Y axis

a= Transformed data used (sq rt transformation)

b= Transformed data used (log 10 transformation)

Individual Tests, FACT-Cog, PCI, PCA). Linear relationships were found between FACT-Cog Total and subscales and the PROMIS Scales (R^2 ranged from 0.219-0.413); PSQI Total (R^2 ranged from 0.18-0.0.24); UCLA-R (R^2 ranged from 0.178-0.267); PSS (R^2 ranged from 0.333-0.45); but not between the FACT-Cog and IPAQ scales. Very small linear or non-linear relationships were found, between all the predictors and the cognitive performance measures, however those relationships between the behavioral variables (sleep and physical activity) appeared the largest. The R^2 values for each scatterplot are displayed in Table 4.8 below.

Covariate Selection

The literature presented in Chapter 2 supports the likelihood that certain individual treatment factors (abdominal obesity, a history of anthracycline based chemotherapy, and treatment with tamoxifen) could explain differences in either cytokine concentrations or cognitive functioning. Therefore, the sample was dichotomized into anthracycline (coded 1) versus non-anthracyclione (coded 0) and independent t tests were run on the outcome variables (cytokines, cognitive function) to see if group differences in these variables exist. The same was done for the sample based on tamoxifen treatment (coded 1), no tamoxifen treatment (coded 0), and for the presence of abdominal obesity, defined as a HWR >0.80 (coded 1), or less that 0.80 (coded 0). An additional t test was run on pre menopausal (coded 0) and post menopausal (coded 1) women because post menopausal status, and subsequent lower levels of estrogen, have been associated with cognitive deficits and brain atrophy in the literature (Eberling, 2004). The independent t test results are displayed in Appendix P**.** One significant group differences was found between those who had undergone anthracycline-based chemotherapy and those who had

Table 4.8

R^2 values for Scatterplot Line of Best fit (Linear and Cubic) Between Individual Factors, Predictor Variables and Cognitive Measures (N=75)

	HVLT-I	HVLT-D	COWAT	TMT A[a]	TMT B[b]	FACT- Cog	PCI	PCA
PROMIS Anxiety	R^2 Lin = .000 R^2 Cub =.051	R^2 Lin = .002 R^2 Cub =.033	R^2 Lin = .015 R^2 Cub =.035	R^2 Lin = .002 R^2 Cub=.017	R^2 Lin = .001 R^2 Cub =.013	R^2 Lin = .362	R^2 Lin = .315	R^2 Lin = .257
PROMIS Depressive	R^2 Lin = .000 R^2 Cu =.057	R^2 Lin =.001 R^2 Cub =.046	R^2 Lin = .017 R^2 Cub =.019	R^2 Lin = .015 R^2 Cub =.062	R^2 Lin = .007 R^2 Cub =.027	R^2 Lin = .315	R^2 Lin = .268	R^2 Lin = .219
PROMIS Fatigue	R^2 Lin = .007 R^2 Cub =.045	R^2 Lin = .000 R^2 Cub =.006	R^2 Lin = .014 R^2 Cub =.042	R^2 Lin = .000 R^2 Cub =.010	R^2 Lin = .009 R^2 Cub =.069	R^2 Lin = .413	R^2 Lin = .364	R^2 Lin = .330
PSQI Total	R^2 Lin = .007 R^2 Cub =.039	R^2 Lin = .030 R^2 Cub =.060	R^2 Lin = .002 R^2 Cub =.005	R^2 Lin = .010 R^2 Cub =.013	R^2 Lin = .009 R^2 Cub=.048	R^2 Lin = .24	R^2 Lin = .225	R^2 Lin = .18
IPAQ Sit Min	R^2 Lin = .001 R^2 Cub =.025	R^2 Lin =.050 R^2 Cub =.081	R^2 Lin = .000 R^2 Cub =.037	R^2 Lin = .007 R^2 Cub =.021	R^2 Lin =.001 R^2 Cub =.026	R^2 Lin = .008 R^2 Cub =.012	R^2 Lin = .019 R^2 Cub =.023	R^2 Lin = .002 R^2 Cub =.006
IPAQ Active Min	R^2 Lin = .011 R^2 Cub =.013	R^2 Lin = .062 R^2 Cub =.129	R^2 Lin = .025 R^2 Cub =.038	R^2 Lin = .037 R^2 Cub =.050	R^2 Lin = .069 R^2 Cub =.080	R^2 Lin= .001 R^2 Cub =.007	R^2 Lin = .001 R^2 Cub =.004	R^2 Lin = .000 R^2 Cub =.004
UCLA-R	R^2 Lin = .018 R^2 Cub =.026	R^2 Lin = .001 R^2 Cub =.026	R^2 Lin = .014 R^2 Cub =.028	R^2 Lin = .004 R^2 Cub =.021	R^2 Lin = .009 R^2 Cub =.012	R^2 Lin = .267	R^2 Lin = .265	R^2 Lin = .178
PSS	R^2 Lin = .004 R^2 Cub =.074	R^2 Lin = .001 R^2 Cub =.076	R^2 Lin = .038 R^2 Cub=.058	R^2 Lin = .029 R^2 Cub =.077	R^2 Lin = .010 R^2 Cub =.123	R^2 Lin = .45	R^2 Lin = .400	R^2 Lin = .333
ESS	R^2 Lin = .011 R^2 Cub =.013	R^2 Lin = .027 R^2 Cub=.133	R^2 Lin = .031 R^2 Cub =.059	R^2 Lin = .029 R^2 Cub =.044	R^2 Lin = .018 R^2 Cub =.045	R^2 Lin = .189	R^2 Lin = .201	R^2 Lin = .145

Note. Line of best fit added to each scatterplot to determine nature of relationship with highest R^2. Cubic $R^2 \geq$ Quadratic R^2 in all the scatterplots;

Table 4.8 (continued)

therefore only Linear and Cubic R^2 included in table. If a linear relationship had a R^2>.010, it was included in the table.
a= Transformed data used (sq rt transformation)
b= Transformed data used (log 10 transformation)
R^2 Lin= R^2 Linear
R^2 Cub= R^2 Cubic

not in Trails A (transformed data, $t = 2.51$, $p = 0.03$). One significant group difference was found between those with abdominal obesity and those without in TNF-α levels ($t = 2.24$, $p = 0.04$).

There was not a consistent pattern in terms of correlations between individual factors, cytokines and cognitive outcomes. The largest correlation between individual factors and cytokine levels was between BMI and TNF-α (Table 4.3). The largest correlations between individual factors and cognitive outcomes were between age, years of education, BMI, and cognitive function measures (presented in Table 4.5 above). Although the original data analysis plan included controlling for individual factors as covariates in step 1 of hierarchical multiple regression analyses, the preliminary analyses for aims 1 and 2 clearly illustrated non-linear relationships, thus hierarchical multiple regressions were not used for aims 1 and 2, and covariates not selected for entry in Step 1.

Non-linear (curvilinear) regression models were used instead for aims 1 and 2, and covariates were not used in these models. First, simple non-linear (cubic) regression models were used to determine the variance of inflammatory factors explained by psychosocial and behavioral factors. These curvilinear (cubic function) regression analyses were exploratory in nature; therefore, no specific hypotheses were tested. Additionally, beta weights were not examined or included because the beta weights of cubic functions are not meaningful for interpretation (Cohen, 2003.). This process was repeated to determine the variance of cognitive outcomes explained by inflammatory factors.

Covariates for aim 3 hierarchical regression were selected based on exploratory correlation analyses, significant t tests, and those individual factors that had the largest correlations with cognitive outcomes. Separate covariates were chosen for aim 3

depending on the cognitive variable used as the dependent variable in the regression models and are displayed in a table in Appendix Q.

Homoscedasticity. For Aim 3 Hierarchical Regression Analyses, scatter plots of the residuals as a function of $\hat{Y}$ were used in order to verify if the assumption of homoscedasticity—whether the errors in estimation are equally variable conditioned on the predicted outcome variable. The residuals for each regression model were plotted (Yplot ZRESID, Xplot ZPRED), then a line of best fit added, and the distance between the line and the actual residuals visually examined. A sign of heteroscedasticity, or a violation of homoscedasticity, is a funnel shaped distribution of the residuals around the line of best fit. Simulation research suggests that small violations of this assumption do not affect the validity of statistical inference, but that more severe violations of this assumption impact inference through its effects on standard error of the regression coefficient (Hayes, 2013). These assumptions were checked with each regression analysis and are displayed within the findings tables.

Regression Diagnostics. Durban Watson values were examined to ensure that residuals were independent, and there was no autocorrelation occurring. These values were deemed "problematic" if they were less than one or greater than three (Plitcha, 2013). Colinieality diagnositics were also conducted using tolerance and variance inflation factor (VIF) values for each of the predictors in the regression models. A general rule of thumb is that tolerance should be greater than 0.1 or 0.2 or that VIF should be less that 10 for all variables. The values for all of these diagnostics within each regression analyses were deemed acceptable and are included in each of the multiple regression tables in the findings.

Findings

The findings from the univariate analyses, correlation analyses, and assumption checks informed the choices for multivariate analyses used to address each aim. The theoretical model depicted in Chapter 1, Figure 1.1, was refined based on these analyses and is shown below in Figure 4.6. Specifically, the individual factor of history of tamoxifen was removed from the model. Pieces of the full model were evaluated separately in the data analyses depending on the aim that was being addressed and are illustrated within each section below (Figures 4.7-4.17). The decision making process will be explained for each of the models in each section below.

Aim 1: To assess the impact of psychosocial (stress, social isolation) and behavioral (physical activity, sleep quality) factors on inflammatory markers (IL-6, TNF-α) after controlling for selected individual factors.

The original data analysis plan for Aim 1 included hierarchical multiple regression. First, bivariate correlational analyses were conducted between psychosocial (stress, social isolation), behavioral (physical activity, sleep quality) factors and inflammatory markers (IL-6, TNF-α) and showed very small, non-significant, or no relationships (Table 4.4). Next, scatter plots were constructed to further evaluate the nature of these relationships and showed that cubic functions better fit the data between the psychosocial factors and cytokines, and the behavioral factors and the cytokines (Table 4.7). Next, all the predictor variables (psychosocial and behavioral) were median centered and bivariate correlation analyses were repeated, but the correlations remained very small, and non-significant. Thus, it was determined that the hypotheses originally proposed could not be evaluated. Instead the following research questions were addressed using the conceptual models below.

Figure 4.6 Refined Biobehavioral Model for BCS

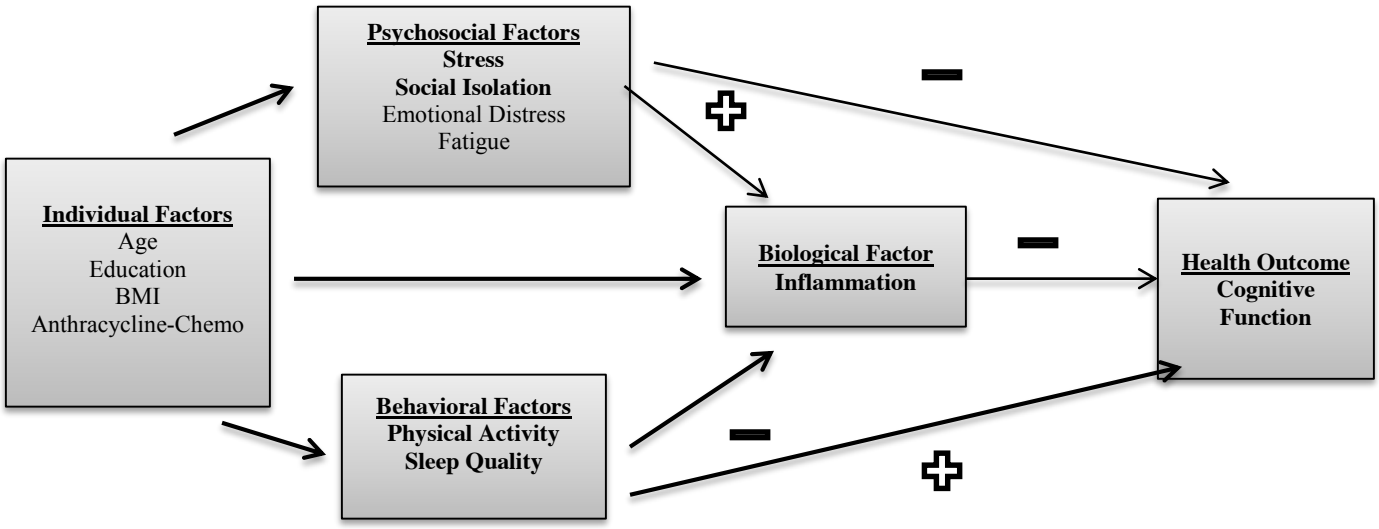

Figure 4.6. Refined conceptual model used for the data analyses for aims 1-6. Individual Factors, Psychosocial Factors, Behavioral Factors, and Biological factors are all predictors of the Health Outcome, Cognitive Function. Individual Factors, Psychosocial Factors, Behavioral Factors are predictors of the Biological Factor as well. Developed from the theoretical model proposed by Kang et al (2010).

RQ 1.1: Are stress, social isolation, physical activity, and sleep quality significant predictors levels of IL-6 concentrations?

RQ 1.2: Are stress, social isolation, physical activity, and sleep quality significant predictors levels of TNF-α concentrations?

For RQ 1.1, the conceptual model from Figure 4.7 was used. Simple and multiple non-linear regression models were used to answer these research questions. No individual factors were selected as covariates in this model, because there were no significant correlations identified between IL-6 and any of the individual factors as seen in Table 4.3. The predictor variables stress, social isolation, physical activity, and sleep quality were operationalized using PSS, UCLA-R, IPAQ Tot Act Min, IPAQ Tot Min Sit, PSQI Total and ESS total. In order to reduce the number of statistical tests, and because of the focus of this study on factors other than emotional distress and fatigue, the PROMIS scales were not evaluated as predictors in these simple non-linear regression analyses.

First, each of the predictor variables were entered as independent variables with the $\log_{10}$ IL-6 as the dependent variable in separate curvilinear regression models, using cubic functions. The results of these analyses are displayed in Table. 4.9 and include the R^2, adjusted R^2, Standard Error, F statistic, and p values. ESS significantly explained 11% of the variance in $\log_{10}$ IL-6 ($p<0.05$). The other predictors, UCLA-R, PSS, IPAQ, and PSQI total did not significantly explain any of the variance of IL-6. Multiple non-linear regression with IL-6 as a dependent variable was not conducted based on the results of the simple regression analyses— only one predictor significantly explained any variance in IL-6 concentrations.

To evaluate RQ.1.2, a conceptual model with TNF-α as the dependent variable was used and is displayed in Figure 4.8. The predictor variables stress, social isolation, physical activity, and sleep quality were operationalized using PSS, UCLA-R, IPAQ Tot

Figure 4.7 Conceptual Model used for Non-Linear Regression Model with log_{10}IL-6 as the Dependent Variable [RQ 1.1]

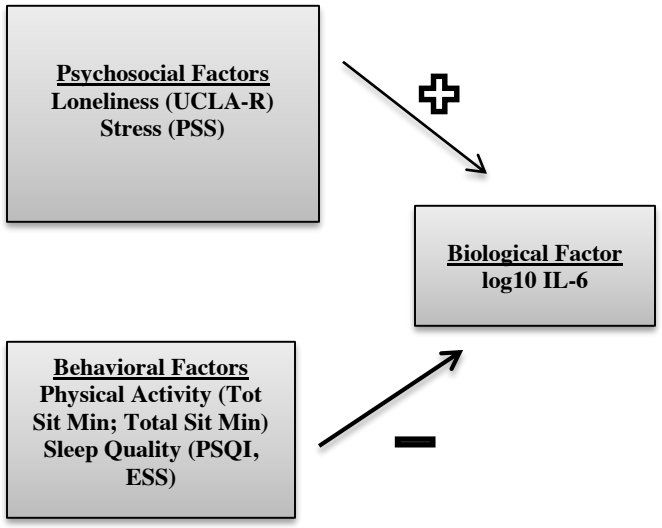

Figure 4.7: Part of conceptual model used to answer RQ 1.1. All independent variables entered into separate non-linear regressions with IL-6 as the dependent variable.

Table 4.9

Curvilinear Simple Regression Models with log10 IL-6 as Dependent Variable (n=66)

IV	R^2	Adj R^2	St.E	F	Sig
UCLA	.036	-.11	.45	0.78	.513
PSS	.050	.004	.44	1.08	.360
IPAQ Act Min	.096	.052	.43	2.19	.098
IPAQ Min Sit	.027	-.02	.44	0.58	.628
PSQI	.006	-.42	.45	0.13	.940
ESS	.15	.11	.42	3.61	.018

Note. Each IV was entered into separate regression models

Act Min, IPAQ Tot Min Sit, PSQI Total and ESS total. In order to reduce the number of statistical tests, and because of the focus of this study on factors other than emotional distress and fatigue, the PROMIS scales were not evaluated in these simple non-linear regression analyses.

Each of the predictor variables were entered as independent variables with the $\log_{10}$ TNF-α as the dependent variable in separate curvilinear regression models, using cubic functions. The results of these analyses are displayed in Table. 4.10 and include the R^2, adjusted R^2, Standard Error, F statistic, and p values. Only 7.1% of the variance in TNF-α was explained by IPAQ Min sitting, but this predictor only approached significance ($p<0.10$). Multiple non-linear regression with TNF-α as a dependent variable was not conducted based on the results of the simple regression analyses— none of the predictor significantly explained any variance in TNF-α concentrations.

Aim 2: To assess the impact of inflammatory markers (IL-6, TNF-α, IL-6* TNF α) on cognitive function (cognitive performance, perceived cognitive functioning) after controlling for selected individual factors.

The original data analyses plan for Aim 2 included hierarchical multiple regression. First, bivariate correlational analyses were conducted between inflammatory markers (IL-6, TNF-α, IL-6*TNF-α) and cognitive function (cognitive performance, perceived cognitive functioning) and showed very small, non-significant, or no relationships (Table 4.4). Next, scatter plots were constructed to further evaluate the nature of these relationships and showed that cubic functions better fit the data between the cytokines and cognitive outcomes (Table 4.7). Next, all the predictor variables (IL-6, TNF-α, L-6* TNF-α) were median centered and bivariate correlations were repeated, but the correlations remained very small, and non-significant. Thus, it was determined that

Figure 4.8 Conceptual Model used for Non-Linear Regression Model with $\log_{10}$ TNF-α as the Dependent Variable [RQ 1.2]

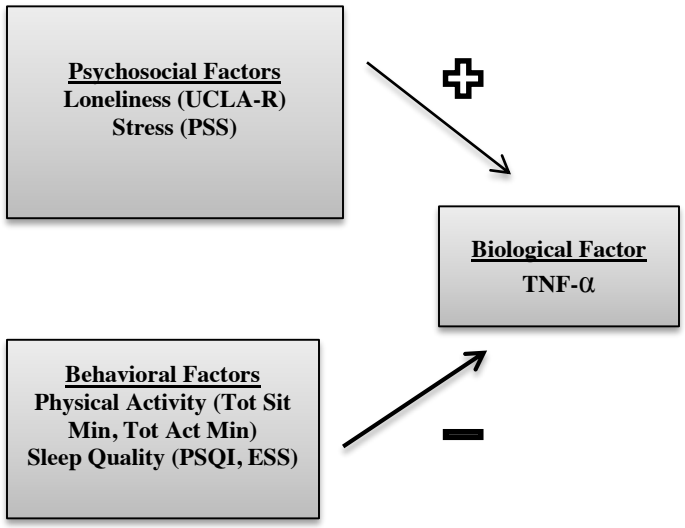

Figure 4.8. Part of Conceptual Model used to answer RQ 1.2. Would have controlled for BMI due to the relationship with TNF- α (r=0.26, p< 0.05), but could not in the non-linear model. No covariates in this model due to limitations of non-linear regression modeling. All independent variables entered into separate non-linear regressions with TNF-α as the dependent variable.

Table 4.10

Curvilinear Simple Regression Models with log_{10}TNF-α as Dependent Variable (n=66)

IV	R^2	Adj R^2	St.Er
UCLA	.018	-.029	.105
PSS	.048	.002	.103
IPAQ Act Min	.015	-.032	.105
IPAQ Min Sit	.114	.071	.10
PSQI	.039	-0.008	.104
ESS	.032	-0.015	.104

Note. Each IV was entered into separate regression models

the hypotheses originally proposed could not be evaluated. Instead the following research questions were addressed using the conceptual models below in Figures 4.9 to 4.14:

RQ 2.1: Are IL-6 and TNF-α significant predictors of perceived cognitive function?

RQ 2.2: Are IL-6 and TNF-α significant predictors of immediate verbal memory performance?

RQ 2.3: Are IL-6 and TNF-α significant predictors of delayed verbal memory performance?

RQ 2.4: Are IL-6 and TNF-α significant predictors of verbal fluency performance?

RQ 2.5: Are IL-6 and TNF-α significant predictors of attention performance?

RQ 2.6: Are IL-6 and TNF-α significant predictors of executive functioning performance

For R.Q 2.1, the conceptual model from Figure 4.9 was used, where FACT-Cog Total was the dependent variable. Each of the cytokines (IL-6, TNF-α, IL-6*TNF-α) were entered separately as independent variables in separate curvilinear regression models, using cubic functions. The results of these analyses are displayed in Table. 4.11 and include the R^2, adjusted R^2, Standard Error, F statistic, and p values. None of the predictor variables explained significant variance in FACT-Cog Total Scores, therefore, multiple non-linear regression with FACT-Cog as a dependent variable was not conducted.

For Research Question 2.2, the conceptual model from Figure 4.10 was used, where HVLT-I was the dependent variable. Each of the predictor variables IL-6, TNF-α, and the interaction of IL-6 and TNF-α were entered as independent variables with

Figure 4.9 Conceptual Model used for Non-Linear Regression Model FACT-Cog Dependent Variable [RQ 2.1]

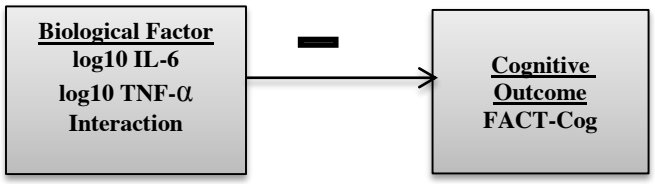

Figure 4.9 Part of the conceptual model used to answer RQ 2.1. Cytokines were predictors of perceived cognitive function in this model. No covariates were included in the model due to limitations of non-linear regression modeling.

Table 4.11

Curvilinear Simple Regression Models with FACT-Cog as Dependent Variable (n=66)

IV	R^2	Adj R^2	St.E	F	Sig
log_{10}IL-6	.005	-.043	35.619	0.10	.96
log_{10}TNF- α	.046	.015	34.6	1.5	.23
log_{10}IL6* log_{10}TNF-α	.003	-.046	35.37	0.05	.98

Note. Each IV was entered into separate regression models

Figure 4.10 Conceptual Model used for used for Non-Linear Regression Model HVLT-I as Dependent Variable [RQ 2.2]

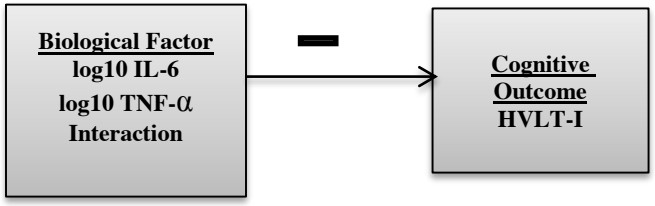

Figure 4.10 Part of the conceptual model used to answer RQ 2.2. Cytokines were predictors of immediate verbal memory recall (HVLT-I) in this model. No covariates were included in the model due to limitations of non-linear regression modeling.

HVLT-I scores as the dependent variable in separate curvilinear regression models, using cubic functions. The results of these analyses are displayed in Table. 4.12 and include the R^2, adjusted R^2, Standard Error, F statistic, and p values. None of the predictor variables explained significant variance in HVLT-I Scores; therefore, multiple non-linear regression with HVLT-I as a dependent variable was not conducted.

For Research Question 2.3, the conceptual model from Figure 4.11 was used, where HVLT-D was the dependent variable. Each of the predictor variables IL-6, TNF-α, and the interaction of IL-6 and TNF-α were entered as independent variables with HVLT-D scores as the dependent variable in separate curvilinear regression models, using cubic functions. The results of these analyses are displayed in Table 4.13 and include the R^2, adjusted R^2, Standard Error, F statistic, and p values. TNF-α explained 8.4% of the variance in HVLT-D Scores ($p< 0.05$). Multiple non-linear regression with HVLT-D as a dependent variable was not conducted based on the results of the simple regression analyses— only one predictor significantly explained any variance in HVLT-D scores.

For Research Question 2.4, the conceptual model from Figure 4.12 was used, where COWAT was the dependent variable. Each of the predictor variables IL-6, TNF-α, and the interaction of IL-6 and TNF-α were entered as independent variables with COWAT scores as the dependent variable in separate curvilinear regression models, using cubic functions. The results of these analyses are displayed in Table 4.14 and include the R^2, adjusted R^2, Standard Error, F statistic, and p values. None of the predictor variables explained significant variance in COWAT Scores; therefore, multiple non-linear regression with COWAT Scores as a dependent variable was not conducted.

For Research Question 2.5, the conceptual model from Figure 4.13 was used, where Trails A was the dependent variable. Each of the predictor variables IL-6, TNF-α,

Table 4.12

Curvilinear Simple Regression Models with HVLT-I as Dependent Variable (n=66)

IV	R^2	Adj R^2	St.E	F	Sig
log_{10}IL-6	.045	-.002	3.60	.963	.42
log_{10}TNF- α	.028	-.002	3.6	.92	.40
log_{10}IL6* log_{10}TNF-α	.034	-.013	3.6	.73	.54

Note. Each IV was entered into separate regression models

Figure 4.11 Conceptual Model used for used for Non-Linear Regression Model HVLT-D as Dependent Variable [RQ 2.3]

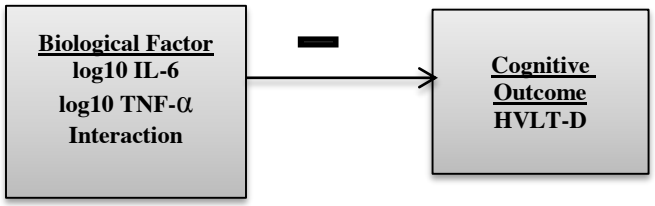

Figure 4.11 Part of the conceptual model used to answer RQ 2.3. Cytokines were predictors of delayed verbal memory recall (HVLT-D) in this model. No covariates were included in the model due to limitations of non-linear regression modeling.

Table 4.13

Curvilinear Simple Regression Models with HVLT-D as Dependent Variable (n=66)

IV	R^2	Adj R^2	St.E	F	Sig
log_{10}IL-6	.040	-.006	1.47	0.87	.46
log_{10}TNF- α	.113	.084	1.4	3.99	.02
log_{10}IL6* log_{10}TNF-α	.020	-.027	1.49	0.43	.73

Note. Each IV was entered into separate regression models

Figure 4.12 Conceptual Model used for used for Non-Linear Regression Model COWAT as Dependent Variable [RQ 2.4]

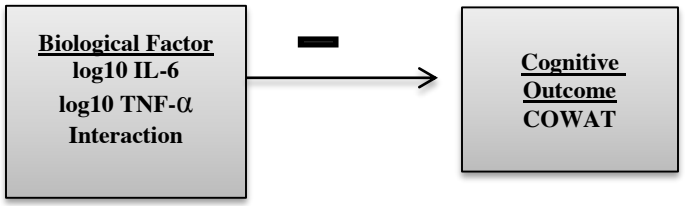

Figure 4.12 Part of the conceptual model used to answer RQ 2.4. Cytokines were predictors of verbal fluency (COWAT) in this model. No covariates were included in the model due to limitations of non-linear regression modeling.

Table 4.14

Curvilinear Simple Regression Models with COWAT as Dependent Variable (n=66)

IV	R^2	Adj R^2	St.E	F	Sig
log_{10}IL-6	.022	-.025	11.43	0.46	.71
log_{10}TNF- α	.062	.033	11.1	2.10	.13
log_{10}IL6* log_{10}TNF-α	.031	-.016	11.28	0.65	.58

Note. Each IV was entered into separate regression models

Figure 4.13 Conceptual Model used for used for Non-Linear Regression Model Trails A as Dependent Variable [RQ 2.5]

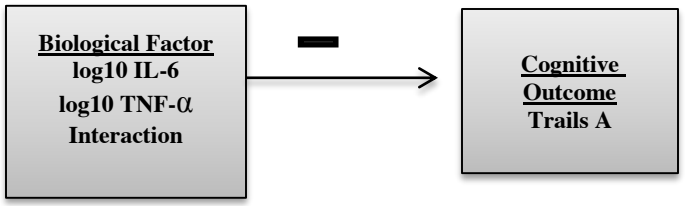

Figure 4.13 Part of the conceptual model used to answer RQ 2.5. Cytokines were predictors of attention (Trails A) in this model. No covariates were included in the model due to limitations of non-linear regression modeling. Transformed Trails A scores were used.

and the interaction of IL-6 and TNF-α were entered as independent variables with Trails A scores as the dependent variable in separate curvilinear regression models, using cubic functions. The results of these analyses are displayed in Table. 4.15 and include the R^2, adjusted R^2, Standard Error, F statistic, and p values. None of the predictor variables explained significant variance in Trails A Scores; therefore, multiple non-linear regression with Trails A as a dependent variable was not conducted.

For Research Question 2.6, the conceptual model from Figure 4.14 was used, where Trails B was the dependent variable. Each of the predictor variables IL-6, TNF-α, and the interaction of IL-6 and TNF-α were entered as independent variables with Trails B scores as the dependent variable in separate curvilinear regression models, using cubic functions. The results of these analyses are displayed in Table. 4.19 and include the R^2, adjusted R^2, Standard Error, F statistic, and p values. None of the predictor variables explained significant variance in Trails B Scores; therefore, multiple non-linear regression with Trails B as a dependent variable was not conducted.

Aim 3: To explore direct and indirect (through inflammatory mediators IL-6 and TNF-α) effects of psychosocial (stress, social isolation) and behavioral (physical activity, sleep quality) factors on cognitive function (memory, attention, processing speed, executive function performance, perceived cognitive function) after controlling for selected individual factors.

The original data analysis plan for Aim 3 was adjusted based on the results from the univariate and correlational analyses, and the findings from the data analyses in Aims 1 & 2. The mediation analyses originally proposed to examine the indirect effects of the predictor variables through inflammatory mediators on cognitive outcomes, could not be conducted due to violation of linearity already discussed at length above. Instead, research questions were developed to examine the direct effects of psychosocial (stress, and social isolation) and behavioral (physical activity, sleep quality)

Table 4.15

Curvilinear Simple Regression Models with Trails A as Dependent Variable (n=66)

IV	R^2	Adj R^2	St.E	F	Sig
log_{10}IL-6	.025	-.022	0.85	0.54	.65
log_{10}TNF- α	.001	-.031	0.85	0.02	.98
log_{10}IL6* log_{10}TNF-α	.032	-.015	0.85	0.67	.57

Note. Each IV was entered into separate regression models

Figure 4.14 Conceptual Model used for used for Non-Linear Regression Model Trails B as Dependent Variable [RQ 2.6]

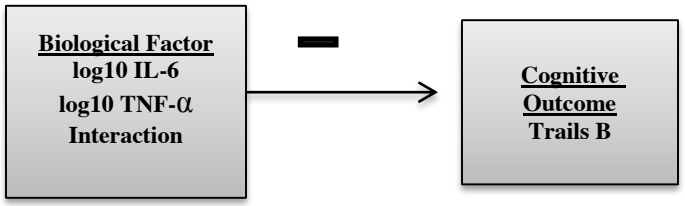

Figure 4.14 Part of the conceptual model used to answer RQ 2.6. Cytokines were predictors of executive functioning performance (Trails B) in this model. No covariates were included in the model due to limitations of non-linear regression modeling. Transformed Trails B scores were used

Table 4.16

Curvilinear Simple Regression Models with Trails B as Dependent Variable (n=66)

IV	R^2	Adj R^2	St.Er	F	Sig
log_{10}IL-6	.037	-.010	0.14	0.79	.50
log_{10}TNF- α	.026	-.005	0.14	0.83	.44
log_{10}IL6* log_{10}TNF-α	.045	-.002	0.14	0.93	.42

Note. Each IV was entered into separate regression models

factors on cognitive function (perceived cognitive function, memory, attention, processing speed, executive function performance) after controlling for selected individual factors. Since these analyses excluded the inflammatory markers, the larger sample (N=75) was used to increase the power of the analyses. The bivariate correlations from Table 4.5 along with some additional correlational analyses between all the PSQI subscales and the cognitive outcomes (Appendix R) informed the development the following research questions:

RQ 3.1: Will psychosocial variables (stress, social isolation) predict perceived cognitive function after controlling for BMI, emotional distress, and fatigue?

RQ 3.2: Will behavioral variables (physical activity and sleep quality) predict perceived cognitive function after controlling for BMI, emotional distress, and fatigue?

RQ 3.3: Will behavioral variables (physical activity and sleep quality) predict delayed verbal memory cognitive performance after controlling for age, and education?

RQ 3.4: Which of the behavioral variables (of physical activity and sleep quality) will predict executive functioning performance after controlling for age?

For RQ's 3.1 and 3.2, the conceptual model depicted in Figure 4.15 was used. BMI was the selected individual factor and entered in Step 1. The PROMIS Scales evaluating anxiety, depression and fatigue were entered in Step 2 since they had large correlations with FACT-Cog. Then PSS, UCLA-R, and PSQI scores were entered into Step 3 to determine if any additional variance in FACT-Cog scores were significantly explained by these variables. The hierarchical regression model results are displayed in Table 4.17. The PROMIS Scores explained an additional 57.3% of the variance in FACT-Cog scores over that of BMI alone (p<0.001). PROMIS Anxiety and Fatigue scales remained significant predictors ($p's$<0.01) when simultaneously entered into Step 2. More perceived anxiety significantly predicted lower scores on FACT-Cog (β=-0.40,

Figure 4.15 Conceptual Model used for Hierarchical Multiple Regression for Perceived Cognitive Function as DV (RQ 3.1- 3.2)

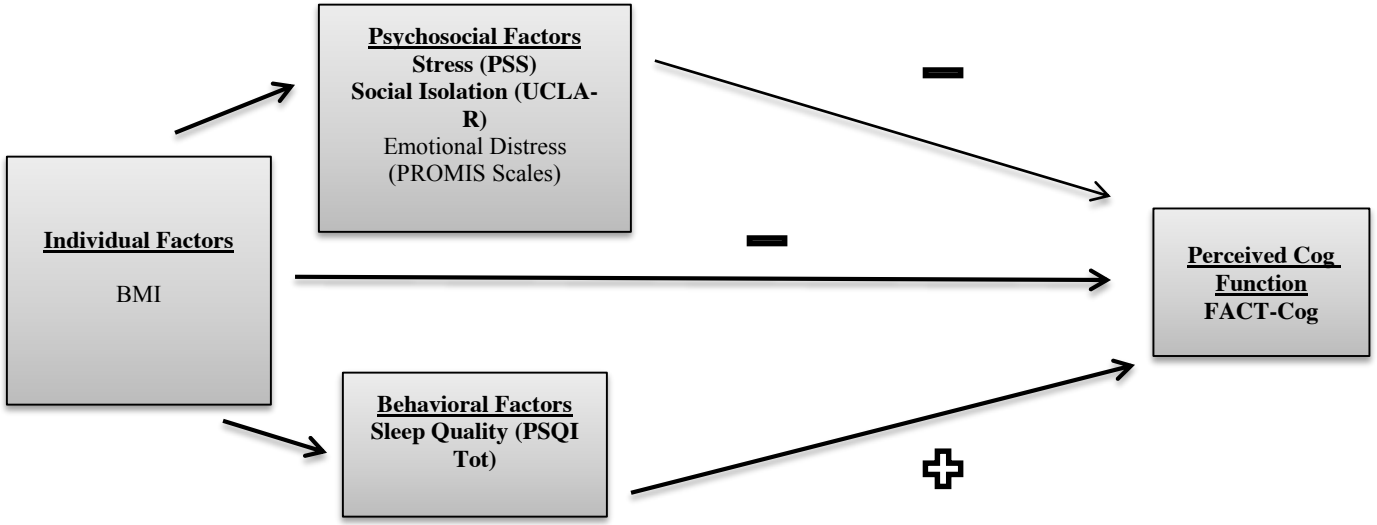

Figure 4.15 Part of the conceptual model used for hierarchical multiple regression for perceived cognitive function as dependent variable to address RQ's 3.1- 3.2.
DV: FACT-Cog Scores
Step 1: Covariates selected BMI (r=-.23, p<.001),
Step 2: Emotional Distress and Fatigue factors entered (PROMIS anxiety, depression, fatigue)
Step 3: Stress, Social Isolation, and Sleep (no significant relationship between IPAQ and Fact Cog, so it was not included in the model)

Table 4.17

Hierarchical Multiple Regression with FACT-Cog Total Score as Dependent Variable (N=75)

		B	*SE B*	*β*	t	*p*	R^{2*}	*p*	ΔR^2	*p*
Step 1	BMI	-1.44	0.71	-0.23	-2.02	.047	0.04	0.047	-	-
Step 2	*PROMIS Anxiety*	*-1.66*	*0.46*	*-0.40*	*-3.40*	*.001*				
	PROMIS Depressive	-0.45	0.64	-0.09	-0.79	0.49				
	PROMIS Fatigue	*-1.83*	*0.36*	*-0.43*	*-5.07*	*.000*	*0.61*	*.000*	*0.573*	*.000*
Step 3	*PSS*	*-0.99*	*0.54*	*-0.24*	*-1.84*	*0.07*				
	UCLA-R	-0.39	0.33	-0.13	-1.20	0.24				
	PSQI	0.36	0.81	0.05	0.45	0.66	0.626	.000	.035	.085

Note. Regression Diagnostics: Residuals (Standardized Residuals ranged from -2.83 to 2.08), Durban Watson within range 1-3 (1.77), Cooks distance less than 1 (min 0.00 max 0.20), VIF all values <10, Tolerance all values >0.3, homoscedasticity assumption met

*Adjusted R^2

t=-2.15, *p*<0.01) and more perceived fatigue significantly predicted lower scores on FACT-Cog (*β*=-0.43, *t*=-5.07, *p*<0.001). In Step 3, PSS, UCLA-R and PSQI explained an additional 3.5% of the variance in FACT-Cog scores (*p*=0.085). The only predictor in this step that approached significance was perceived stress (*β*=-0.24, *t*=-1.84, *p*=0.07).

The conceptual model in Figure 4.16 was used for the hierarchical multiple regression to answer RQ 3.3. Age (*r*=-0.26, *p*<.05) and Years of Education (*r*=0.26, *p*<.05) were selected as covariates in this model and entered in Step 1. The predictors with significant correlations with HVLT-D scores were chosen for Step 2 and included IPAQ Min Sit subscale, PSQI total, and ESS Total Scores. Age and Years of education explained 9.5% of the variance in HVLT-D Scores (*p*<0.05). PSQI, ESS and IPAQ scores explained an additional 9.1% of the variance in HVLT-D, and this change in R^2 approached significance (*p*=0.056) The hierarchical regression model results are displayed in Table 4.18. After controlling for age and education, and while holding IPAQ Min sit and ESS constant, PSQI scores approach significance as predictors of verbal memory performance (*β*=-0.20, *t*=-1.84, *p*=0.07).

The conceptual model in Figure 4.17 was used for the hierarchical multiple regression to test hypotheses 3.4. Age (*r*=0.36, *p*<.01) was selected as a covariate in this model and entered in Step 1. The predictors with significant correlations with Trails B scores were chosen for Step 2 and included IPAQ Act Min subscale and PSQI Sleepaid Subscale (correlation can be seen in Appendix "Letter"). Age explained 12% of the variance in Trails B scores (*p*<0.001). ESS and IPAQ scores explained an additional 7.6% of the variance in Trails B (*p*=0.04). Of the two predictors entered in Step 2, IPAQ Active Min approached significance as a predictor of Trails B scores (*β*=000, *t*=1.92, *p*=0.06). These hierarchical regression model results are displayed in Table 4.19. After

Figure 4.16 Conceptual Model used for Non-Linear Regression of Delayed Memory Performance as DV (RQ 3.3)

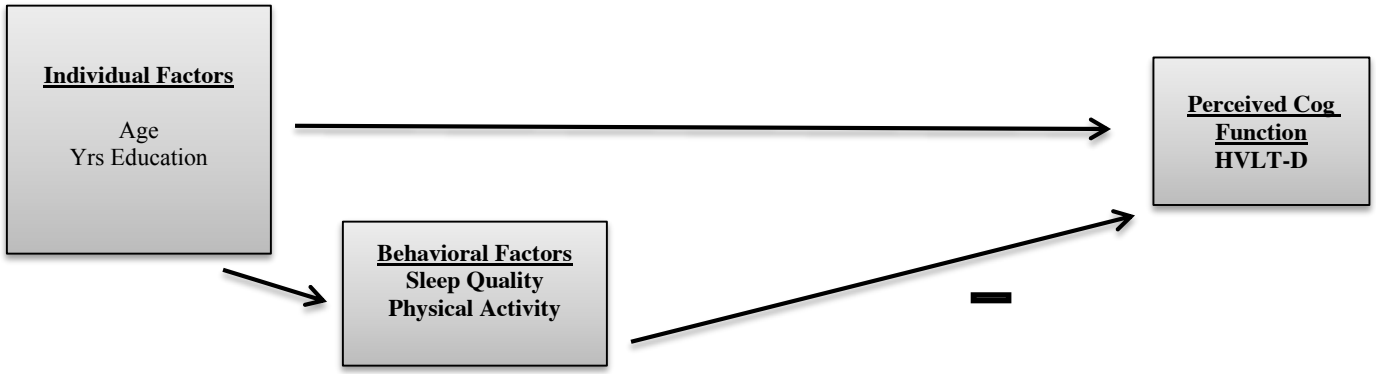

Figure 4.16 Part of the conceptual model used for the non-linear regression of delayed memory performance as the dependent variable to answer RQ 3.3.
DV: HVLT-D scores
Step 1: Covariates selected Age (r=-.26, p < .05), Yrs of Education (r=.26, p< .05) Step 2: (IPAQ Min Sitting), ESS, and PSQI were entered

Table 4.18

Hierarchical Multiple Regression with HVLT-D Score as Dependent Variable (N=75)

		B	*SE B*	*β*	t	*p*	R^{2*}	*p*	ΔR^2	*p*
Step 1	Age	-0.04	0.02	-0.23	-2.05	0.04				
	Yrs Education	0.19	0.09	0.23	2.08	0.04	0.095	0.010		
Step 2	ESS	0.07	0.04	0.17	1.50	0.14				
	PSQI	-0.08	0.04	-0.20	-1.84	0.07				
	IPAQ Min Sit	.00	.00	.14	1.25	0.22	0.153	0.010	0.091	0.056

Note. Regression Diagnostics: Residuals (Standardized Residuals ranged from -2.5 to 1.08), Durban Watson within range 1-3 (1.99), Cooks distance less than 1 (min 0.00 max 0.09), VIF all values <10, Tolerance all values >0.3, homoscedasticity assumption questionable.

*Adjusted R^2

Figure 4.17 Conceptual Model used for Non-Linear Regression of Executive Function Performance as DV (RQ 3.4)

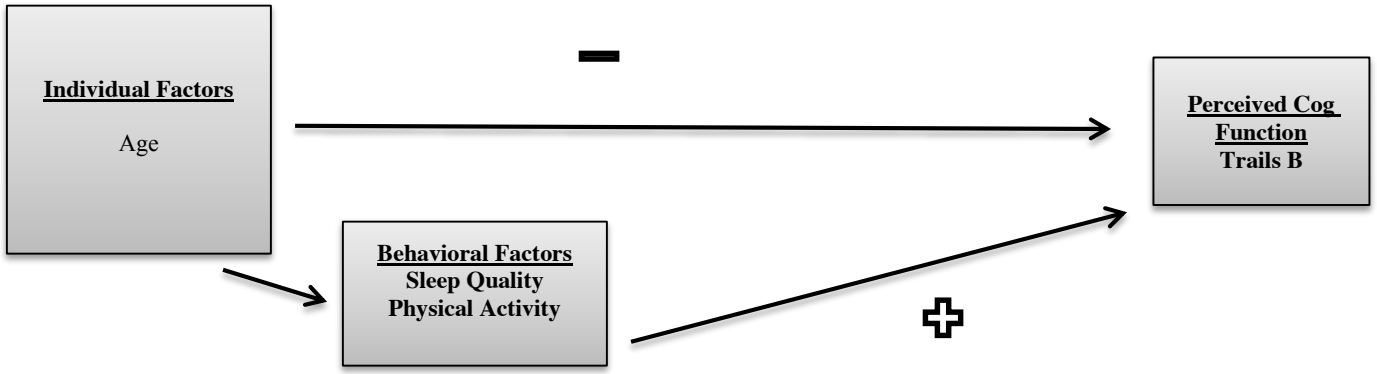

Figure 4.17 Part of the conceptual model used for non-linear regression of executive function performance as the dependent variable to answer RQ 3.4.
DV: Trails B scores
Step 1: Covariates selected Age (r=.36, p< .01)
Step 2: (IPAQ Active Min), PSQI Sleepaid Subscale

Table 4.19

Hierarchical Multiple Regression with Trails B[b] Score as Dependent Variable (N=75)

		B	*SE B*	*β*	t	*p*	R^{2*}	*p*	ΔR^2	*p*
Step 1	Age	0.01	0.00	0.36	3.31	0.001	0.12	0.001		
Step 2	PSQI Sleepaid Subscale	0.02	0.01	0.15	1.36	0.178				
	IPAQ Active Min	0.000	0.000	.021	1.92	0.060	0.17	0.001	0.076	0.04

b= Transformed data used (log 10 transformation)

Regression Diagnostics: Residuals (Standardized Residuals ranged from -1.97 to 3.82), Durban Watson within range 1-3 (1.79), Cooks distance less than 1 (min 0.00 max 0.29), VIF all values <10, Tolerance all values >0.3, homoscedasticity assumption met.

*Adjusted R^2

controlling for age, and holding PSQI Sleepaid subscale constant, physical activity approached significance as a predictor of $\log_{10}$ Trails B scores.

Additional Analyses

Aim 4: To describe the nature of the relationships between psychosocial, behavioral factor and cytokines, and between cytokines and cognitive outcomes.

The results from aims 1 and 2 led to the development of an additional aim to better describe the nature of relationships among the psychosocial factors, behavioral factors and cytokines, and between the cytokines and cognitive outcomes. Two research questions were developed:

RQ 4.1. What patterns of non-linear relationships can be visualized between the psychosocial factors, behavioral factors, and cytokines?

RQ 4.2. What patterns of non-linear relationships can be visualized between the cytokines and cognitive outcomes?

Non-parametric fit lines, specifically Loess, can be used to visualize and understand complex bivariate relationships that may otherwise be missed using traditional parametric tests (Jacoby, 2000). In some cases, locally weighted regression, Loess regression, can yield more information about the true nature of the complex associations than parametric methods. It is said that Loess regression preserves the simplicity of parametric modeling but has more flexibility in terms of parameters and assumptions. Parametric regression modeling fits data to one global function, whereas loess regression fits the data locally—in sequential, weighted, polynomial regression models (Cleveland, 1979; Jacoby, 2000; Tan, 2012). Loess regression uses a mathematical algorithm to follow concentrations of points in a scatter plot along the horizontal axis of the scatter plot, resulting in a line that passes through the most dense spots of the graph regardless of the shape the line makes, using ordinary least squares

(OLS) in sliding windows of the data (Jacoby 2000). This method can characterize almost any relationship and the user controls the degree of smoothing. The major disadvantage of using this method is that inference is not as straight forward as parametric methods because the results of the analyses are graphical in nature, and do not provide interpretable mathematical statistics such as beta weights, p values, or effect sizes. Confidence intervals are often used to serve the purpose of inference and the 95% CI can be fitted around the Loess curve.

Two parameters need to be set before running a Loess regression line in a scatter plot— the span and number of degrees. The span refers to how much data within each "slice" of the scatter plot on the horizontal axis will be used to fit the weighted polynomial regression. It can range from 0.1-1.0, with lower values providing a more exact, or "jagged" line, and higher values providing a "smoother" curved line. There are no strict rules for determining the span. Jacoby (2000) explains that the objective is "to produce a loess curve that is as smooth as possible, but still captures all of the important structure that exists within the data"(p.586). The degree parameter refers to the number of bends in the regression line. After these parameters are set, the loess function will determine the line of best fit based on the locally weighted regression points. For all the scatter plots used to address RQ4.1 and 4.2, a span of 0.50 and degree of 2 was used to fit the Loess line to the data. Additionally, 95% Confidence Intervals were added to the Loess lines in each graph.

For RQ's 4.1, separate scatter plots were created between raw scores of IL-6 (y-axis) and all of the psychosocial and behavioral variables (on the x-axis). Then, separate scatter plots were created between raw scores of TNF-α (y-axis) and all of the psychosocial and behavioral variables (on the x-axis). Scatter plots were constructed

using R studio (2017, Boston, MA) with Loess Regression Lines. An example of one of these graphs is below in Figure 4.18. The remaining graphs can be found in Appendix S.

For RQ's 4.2, separate scatter plots were created between perceived cognitive function (y-axis) and each cytokine (IL-6, TNF-α; y-axis). Then separate scatter plots were created between HVLT-I (y-axis) and each cytokine (IL-6, TNF-α; y-axis), and subsequently with HVLT-D, COWAT, Trails A and Trails B on the y-axes and cytokines on the x axes. Scatter plots were constructed Using R studio (2017, Boston, MA) and Loess Regression Lines added with 95% Confidence intervals. An example of one of these graphs is below in Figure 4.19. The remaining graphs can be found in Appendix T.

Loess modeling was used to explore the complexities of these relationships. These non-parametric analyses illustrated the complex nature of relationships involving cytokines. In this study the relationships overall, have many bends, and further justify the decision to not run linear modeling with these data. The Loess graphs with the cytokines regressed on predictor variables exhibited that linear relationships exist between the variables and cytokine concentrations, but that these relationships change and vary across levels of predictor variables. These relationships appear very steep and strong at certain levels of the predictor variables. Similarly, the Loess graphs with the cognitive outcomes regressed on the cytokine variables showed linear relationships exist between the variables and cognitive function, but that these relationships change and vary across levels of cytokines. These relationships appear very steep and strong at certain levels of the predictor variables. Only graphs between IL-6 and HVLT-I and TNF-α and Trails A and B were essentially straight across all levels of the cytokines suggesting either too much "noise", or error in the data collected or no relationship exists between thee variables.

Figure 4.18 Loess Regression with IL-6 on the Y axis and Perceived Stress on the X Axis

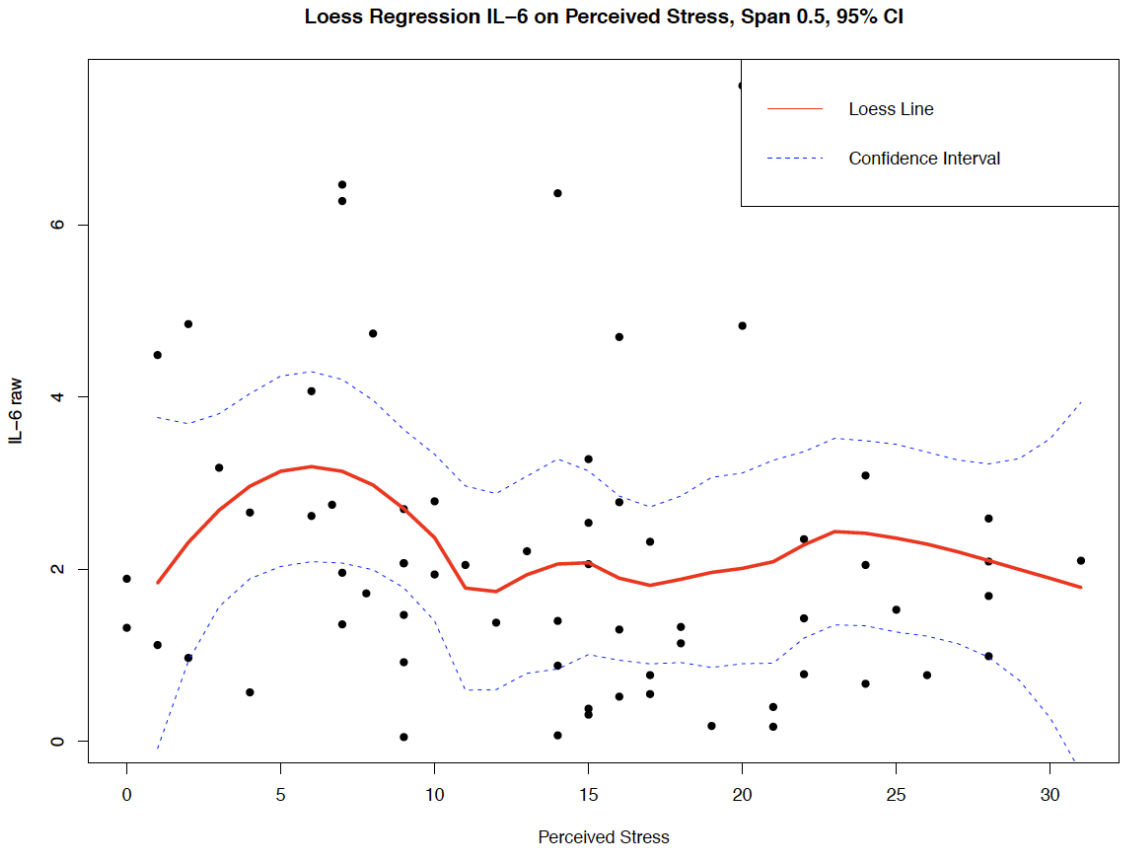

Figure 4.18 Loess Regression with IL-6 on the Y axis and Perceived Stress on the X Axis. Graph created in R Studio, parameters were a span of 0.50 and 2 degrees. The 95% confidence interval is depicted with the blue dotted line above and below the red Loess line.

Figure 4.19 Loess Regression with FACT-Cog on the Y axis and TNF-α on the X Axis

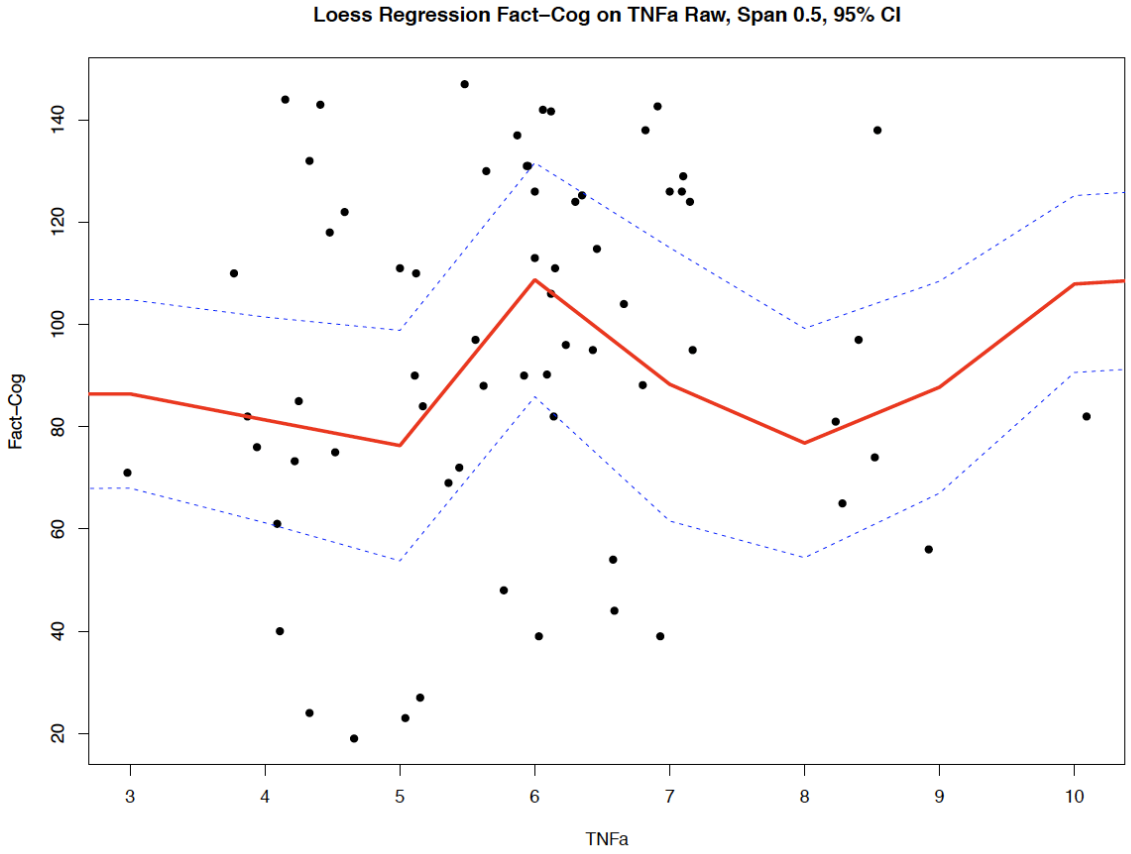

Figure 4.18 Loess Regression with FACT-Cog on the Y-axis and TNF-α on the X-axis. Graph created in R Studio, parameters were a span of 0.50 and 2 degrees. The 95% confidence interval is depicted with the blue dotted line above and below the red Loess line

Aim 5: To explore direct and indirect effects of psychosocial factors (stress, perceived social isolation, emotional distress, and fatigue), and sleep quality on perceived cognitive function

The results from aim 3 showed significant inter-correlations between the psychosocial variables, sleep, and perceived cognitive function; therefore, an additional aim to explore direct and indirect effects of psychosocial factors (stress, perceived social isolation, emotional distress, and fatigue) and sleep on perceived cognitive function was derived. The analyses for this aim included 1) detailed bivariate correlation analyses between the FACT-Cog subscales, the psychosocial predictors, and sleep quality; 2) Hierarchical Multiple regression, and 3) Mediation Analyses using OLS to better understand how the psychosocial and sleep variables influence and perceived cognitive functioning in breast cancer survivors. The full sample (N= 75) was used in these analyses.

Bivariate Pearson's correlations were run between the FACT-Cog total and subscales, PROMIS Anxiety, PROMIS Depression, PROMIS Fatigue, PSS, UCLA-R, and PSQI total and subscales. A Bonferroni adjustment was made to the p value to account for multiple comparisons (Munroe, 2005). Those p values less than 0.0011 were considered significant and are starred in Table 4.20. Similar patterns of moderate to large negative correlations were found between FACT-Cog total, PCI and PCA subscales and the psychosocial and sleep variables (*r's* ranged from -0.39 to -0.74, *p's*< 0.0011). The magnitude of the correlations between the psychosocial variables with the PCA scale was slightly smaller than with the FACT-Cog total and PCI subscales. The subscales of the PSQI that remained significantly related to the FACT-Cog after the Bonferroni correction were between PSQI Efficiency and FACT-Cog (*r*=-0.39), PSIQ Sleep Disturbance and all

Table.4.20

Pearson's Correlations between Psychosocial Variables and FACT-Cog total and Subscales (N=75)

	PCI	PCA	QOL	Comments	FACT-Cog Total
PROMIS Anxiety	-.62*	-.52*	-.74*	-.38*	-.65*
PROMIS Depressive	-.57*	-.50*	-.75*	-.33	-.61*
PROMIS Fatigue	-.61*	-.59*	-.64*	-.49*	-.66*
UCLA-R	-.55*	-.46*	-.55*	-.36	-.56*
PSS	-.68*	-.60*	-.74*	-.46*	-.71*
PSQI Total	-.46*	-.43*	-.45*	-.39*	-.49*
Duration	-.10	-.15	-.13	-.21	-.14
Latency	-.35	-.34	-.34	-.29	-.38*
Efficiency	-.37	-.39*	-.32	-.29	-.39*
Disturbance	-.41*	-.33	-.39*	-.40*	-.43*
Sleepaid	-.20	-.15	-.23	-.05	-.20
Daytime Dysfunction	-.51*	-.33	-.49*	.31	-.49*
Sleep Quality	-.23	-.28	-.16	-.37*	-.26

**p<0.0011 (Bonferroni Correction 0.05/45)*

but the PCA subscale (*r's* -0.39 to -0.43), and PSQI Daytime dysfunction and all but the PCA subscale (*r's* -0.49 to -0.51).

Based on the findings from the bivariate Pearson's correlations, FACT-Cog total scores were chosen as the dependent variable for hierarchical multiple regression Modeling. BMI was selected as a covariate because of its' significant negative relationship with FACT-Cog (r=-0.23, p<0.05). All the PROMIS Scales, PSS, UCLA-R and PSQI were entered in Step 2, in order to determine how much variance was explained by these variables and to explore the unique relationships between the predictor variables while controlling for the other independent variables. The results are displayed in Table 4.21 below. BMI alone explained 4% of the variance in FACT-Cog scores (p = 0.047), and together, the PROMIS Scales, PSS, UCLA-R and PSQI significantly explained an additional 60.8% of the variance in FACT-Cog scores. Controlling for PROMIS Depression, PROMIS Fatigue, PSS, UCLA-R and PSQI, PROMIS Anxiety remained a significant predictor of FACT-Cog (β= *-0.29, t*=-2.02, p= 0.47). Controlling for PROMIS Anxiety, PROMIS Fatigue, PSS, UCLA-R and PSQI, PROMIS Fatigue remained a significant predictor of FACT-Cog (β= *-0.36, t*=-3.04, p= 0.001).

The findings from the hierarchical multiple regression, suggest that the large significant negative relationship between PSS and FACT-Cog (r=-0.71, p<.0011) found in the bivariate correlations analysis might be explained by perceived feelings of anxiety and fatigue. Thus, a mediation analysis using Andrew Hayes' PROCESS macro in SPSS 24.0 was used to test the direct and indirect effects (through feelings of anxiety and fatigue) of perceived stress on perceived cognitive functioning while controlling for BMI. This analysis allows for inferential quantification of the indirect effects on dependent variables through mediator variables (Hayes, 2013). This method utilizes bootstrap confidence intervals to estimate and interpret the effect size of the indirect effects of the

Table 4.21

Hierarchical Multiple Regression with Psychosocial and Sleep Predictors and FACT-Cog Total Score as Dependent Variable (N=75)

		B	*SE B*	*β*	t	*p*	R^{2*}	*p*	ΔR^2	*p*
Step 1	BMI	-1.44	0.71	-0.23	-2.02	.040	0.04	0.047	-	-
Step 2	*PROMIS Anxiety*	*-1.22*	*0.60*	*-0.29*	*-2.02*	*.047*				
	PROMIS Depressive	0.14	0.71	0.03	0.20	0.85				
	PROMIS Fatigue	*-1.53*	*0.45*	*-0.36*	*-3.40*	*.001*				
	PSS	-0.99	0.54	-0.24	-1.84	0.07				
	UCLA-R	-0.39	0.33	-0.13	-1.20	0.24				
	PSQI	0.36	0.81	0.05	0.45	0.66	0.626	.000	.608	.001

Note. Regression Diagnostics: Residuals (Standardized Residuals ranged from -2.83 to 2.08), Durban Watson within range 1-3 (1.77), Cooks distance less than 1 (min 0.00 max 0.20), VIF all values <10, Tolerance all values >0.3, homoscedasticity assumption met

*Adjusted R^2

independent variables on the dependent variables. The direct effects of the independent variable on cognitive function was determined by the regression coefficient magnitude and significance ($p<.05$), and the indirect effects of the perceived anxiety and fatigue were determined by a significant effect size (95% Bootstrap CI does not include "0"). The mediation analysis with multiple mediators is conceptually illustrated in Figure 4.20.

Using the PROCESS Macro in Linear Regression, FACT-Cog was entered as the dependent variable, PSS was entered as the independent variable, PROMIS Anxiety and PROMIS Fatigue as the mediators, and BMI as the covariate. PSS had a significant direct effect on FACT-Cog scores (*direct effect*= -1.21, *bootstrap SE*= 0.51, *t*= -2.42 , *p*= 0.02), meaning that a participant who scores 1 point higher on the PSS scale, scored on average 1.2 points lower on the FACT-Cog. There was a significant negative indirect effect of PSS on FACT-Cog through PROMIS Anxiety (*indirect effect*= -0.85 *bootstrap SE*= 0.45, *95% Bootstrap CI*= -1.81, 0.05), meaning that a participant who scores 1 point higher on PSS scored, on average, 0.85 points lower on FACT-Cog through feelings of anxiety (as measured by PROMIS Anxiety). There was also a significant negative indirect effect of PSS on FACT-Cog through PROMIS Fatigue (*indirect effect*= -0.83 *bootstrap SE*= 0.24, *95% Bootstrap CI*= -0.05, -0.001), meaning that a participant who scores 1 point higher on PSS is estimated to score 0.83 points lower on FACT-Cog through feelings of fatigue (as measured by PROMIS Fatigue). These results suggest that perceived stress has significant, and almost equivalent, indirect effects on perceived cognitive function through both mediators (PROMIS Anxiety, and PROMIS Fatigue).

This multiple mediator analysis was repeated with UCLA-R as the independent variable, to test the direct and indirect effects (through feelings of anxiety and fatigue) of feelings of loneliness on perceived cognitive functioning while controlling for BMI. Using the PROCESS Macro in Linear Regression, FACT-Cog was entered as the

Figure 4.20. Conceptual Multiple Mediator Model

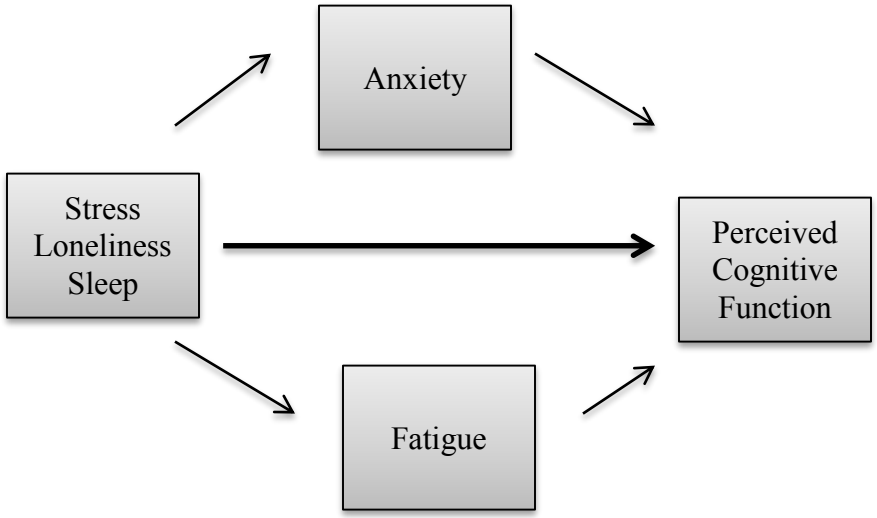

Figure 4.20 Conceptual model used for aim 5 to explore the mediation pathways of perceived stress (PSS), loneliness (UCLA-R), and sleep quality (PSQI) through feelings of anxiety and fatigue (PROMIS scales) as mediators on perceived cognitive function (FACT-Cog). Three separate multiple mediator analyses using ordinary least squares were conducted with stress, loneliness and sleep all as the independent variables. In all three models, anxiety and fatigue were the mediators, and perceived cognitive function (FACT-Cog) the dependent variable.

dependent variable, UCLA-R was entered as the independent variable, PROMIS Anxiety and PROMIS Fatigue as the mediators, and BMI as the covariate. UCLA-R had a direct effect, although not significant, on FACT-Cog scores (*direct effect*= -0.53, *bootstrap SE*= 0.28, *t*= -1.91, *p*= 0.06), meaning that a participant who scores 1 point higher on the UCLA scale, has on average 0.5 points lower on the FACT-Cog. There was a significant negative indirect effect of UCLA-R on FACT-Cog through PROMIS Anxiety (*indirect effect*= -0.59, *bootstrap SE*= 0.16, *95% Bootstrap CI*= -0.95, -0.31), meaning that a participant who scores 1 point higher on UCLA-R is estimated score, on average 0.59 points lower on FACT-Cog through feelings of anxiety (as measured by PROMIS Anxiety). There was also a significant negative indirect effect of UCLA-R on FACT-Cog through PROMIS Fatigue (*indirect effect*=-0.61, *bootstrap SE*= 0.19, *95% Bootstrap CI*= -1.08, -0.30), meaning that a participant who scores 1 point higher on UCLA-R is estimated to score on average 0.83 points lower on FACT-Cog through feelings of fatigue (as measured by PROMIS Fatigue). These results suggest that perceived social isolation has significant, and almost equivalent, indirect effects on perceived cognitive function through both mediators (PROMIS Anxiety, and PROMIS Fatigue).

The multiple mediator analysis was repeated one last time with PSQI as the independent variable, to test the direct and indirect effects (through feelings of anxiety and fatigue) of sleep quality on perceived cognitive functioning while controlling for BMI. Using the PROCESS Macro in Linear Regression, FACT-Cog was entered as the dependent variable, PSQI was entered as the independent variable, PROMIS Anxiety and PROMIS Fatigue as the mediators, and BMI as the covariate. PSQI did not have a significant direct effect on FACT-Cog scores (*direct effect*= 0.36, *bootstrap SE*=0.82, *t*= 0.44, *p*=0.66). However, there was a significant negative indirect effect of PSQI on FACT-Cog through PROMIS Anxiety (*indirect effect*= -1.84, *bootstrap SE*= 0.56, *95%*

Bootstrap CI= -3.07, -0.87), meaning that a participant who scores 1 point higher on PSQI is estimated to score on average, 1.84 points lower on FACT-Cog through feelings of anxiety (as measured by PROMIS Anxiety). There was also a significant negative indirect effect of PSQI on FACT-Cog through PROMIS Fatigue (*indirect effect*= -2.45, *bootstrap SE*= 0.67, *95% Bootstrap CI*= -4.09, -1.43), meaning that a participant who scores 1 point higher on PSQI is estimated to score 2.45 points lower on FACT-Cog through feelings of fatigue (as measured by PROMIS Fatigue). These results suggest that the effects of sleep quality on perceived cognitive function are mediated by feelings of anxiety and fatigue (PROMIS Anxiety, and PROMIS Fatigue), with fatigue having a larger direct effect.

Aim 6: To explore patterns of relationships between cytokines (IL-6, TNF-α) and cognitive measures (FACT-Cog, HVLT-I, HVLT-D, COWAT, Trails A, Trails B) in BCS classified with "mild cognitive impairment" and those classified as "unimpaired".

It is possible that the correlations between cytokines and cognitive function are only present in cognitively impaired individuals, or those in a more pathological physical state, and not present in unimpaired individuals, who are likely in a state of physical homeostasis. Similar patterns of relationships have been reported in the field of persistent fatigue in BCS— significant relationships between peripheral cytokines and behavioral factors in fatigued BCS but not in non-fatigued survivors (Bower & Lamkin, 2013). To explore whether patterns of correlations differed by cognitive impairment status, the sample was divided into "impaired", defined as -1.5 SD below the mean on at least one NP test (n=13), and "unimpaired" individuals (n=53). Non-parametric correlations between the cytokines and cognitive measures were examined in the impaired group using Spearman's rho and Pearson's r correlations were re-examined in the unimpaired group.

The pattern of correlations was in fact different between groups and is displayed in Table 4.22. In the impaired group, large significant negative relationships were found between FACT-Cog and IL-6 (*rho*= -.55, $p < .01$) and the interaction between IL-6 and TNF-α (*rho*= -.60, $p < .01$). In the unimpaired group, no relationships were found between FACT-Cog and IL-6 but there was a moderate positive relationship between TNF-α (*r*= .33, $p < .05$). In the impaired group moderate positive relationships were found between Trails A and the interaction of IL-6 and TNF-α (*rho*= .64, $p < .05$) and Trails B and both TNF-α and the interaction of IL-6 and TNF-α (*rho's*= .54 & .64, *p's*< .05). No significant relationships were found between the cytokines and NP test scores in the unimpaired group. These findings suggest that there may be significant linear relationships between perceived cognitive function (FACT-Cog), executive functioning performance (Trails A and B), and the cytokines (IL-6 and TNF-α) in those BCS who have cognitive impairment.

Differing patterns of correlations were observed in the impaired and unimpaired groups, the relationships among cytokines (IL-6, TNF- α) and individual and predictor variables (age, education, months since chemotherapy, BMI, PROMIS Scales, PSS, UCLA-R, PSQI, ESS, IPAQ) were explored. In the impaired group, a significant positive relationship was found between BMI and IL-6 (*rho*= .58, $p < .05$) and the interaction of IL-6 and TNF-α (*rho*= .65, *p*< .05), suggesting that as BMI increases so does IL-6 in this group. Again, the opposite pattern was observed in the unimpaired group between BMI and IL-6 (*r*= -0.27, $p <0.05$) and the interaction IL-6 and TNF-α (*r*= -0.28, *p*< 0.05) suggesting that as BMI decreases in the unimpaired group, IL-6 levels increase. For the predictor variables, a large positive relationship was observed between daytime sleepiness (ESS) and IL-6 (*rho*= .76, $p < .01$) and the interaction IL-6 and TNF-α (*rho*= .78, $p < .01$) suggesting that as daytime sleepiness worsens, IL-6 levels increase in the

Table. 4.22

Correlations between, Predictor Variables, Cytokines and Cognitive Outcomes in Impaired Group (n=13) and Unimpaired (n=53)

	Impaired (n=13)			Unimpaired (n=53)		
	IL-6ϰ	TNF- αϰ	interactionϰ	IL-6ϰ	TNF- αϰ	interactionϰ
Age	.37	-.11	.35	-.11	-.13	-.13
Education	.10	-.37	.10	.01	.13	-.01
BMI	.58*	.17	.65*	-.27*	.14	-.28*
Months since Chemo	.20	.46	.25	-.06	-.24	-.09
PROMIS Anxiety	.04	.15	-.03	.12	-.09	.10
PROMIS Depressive	.16	.50	.20	.13	-.17	.11
PROMIS Fatigue	.28	.38	.37	-.01	-.25	-.01
PSQI Total	.09	-.03	.08	.04	-.14	.01
IPAQ Sit Min	.01	-.02	.06	-.13	.10	-.14
IPAQ Active Min	.15	-.15	.17	.24	.04	.24
UCLA-R	.24	.19	.24	-.11	-.11	-.11
PSS	.34	-.01	.32	-.19	-.15	-.20
ESS	.76**	.28	.78**	-.37**	-.20	-.36**
FACT-Cog	-.55*	-.48	-.60*	.12	.33*	.13
HVLT-I	.04	-.30	.02	-.15	.06	-.17
HVLT-D	-.17	-.39	-.16	.01	.16	-.02
COWAT	-.19	-.37	-.27	-.04	.01	-.06
Trails A[a]	.48	.30	.54*	-.05	-.02	-.07
Trails B[b]	.45	.64*	.54*	-.02	.07	-.04

Note. Spearman's Rho used for impaired group, Pearson's *R* used unimpaired group. ϰ= log transformed, *a= Transformed data used (square root transformation), b= Transformed data used (log 10 transformation), ** p <.01, * p<.05*

impaired group. The opposite pattern was observed in the unimpaired group between daytime sleepiness (ESS) and IL-6 (r= -.37, p <.01) and the interaction of IL-6 and TNF-α (r= -.36, p< .01) suggesting that as daytime sleepiness worsens, that IL-6 levels decrease. These findings need to be interpreted with caution because of the small sample size.

CHAPTER SUMMARY

The majority of this sample was white, well educated, employed, and financially stable with an average age of 49 years. Most of the women were three years post-chemotherapy completion, had a history of stage II or III invasive ductal carcinoma, and had undergone surgery, chemotherapy, radiation and hormonal therapies. Univariate analyses revealed that the majority of the study variables were psychometrically sound, that the sample fell in the "average" range for most of the self-report measures, and that the participants exhibited average to above average cognitive performance. Prior to conducting regression analyses, assumptions were checked and revealed that the assumption of linearity was violated between all cytokines and other variables. Non-linear (curvilinear) regression models were used for aims 1 and 2 and revealed that 1) only daytime sleepiness, (ESS) significantly explained any variance in IL-6 concentrations; 2) none of the predictors significantly explained any variance in TNF-α concentrations; 3) TNF-α explained 8.4% of the variance in HVLT-D scores; and 4) the cytokines did not explain any variance in FACT-Cog, HVLT-I, COWAT, or Trails A and B scores. For aim 3, hierarchical regression revealed that 1) stress (PSS), loneliness (UCLA-R) and sleep quality (PSQI) significantly explained 3.5% of the variance in perceived cognitive function (FACT-Cog); 2) sleep quality (PSQI), daytime sleepiness (ESS) and physical activity (IPAQ) explained 9.1% of the variance in delayed memory (HVLT-D); and 3) daytime sleepiness (ESS) and physical activity (IPAQ) explained an

additional 7.6% of the variance in executive function performance (Trails B). For aim 4, Loess regression was used to explore the complexities of the relationships between psychosocial and behavioral factors and cytokines and between the cytokines and cognitive measures. These regression lines revealed that linear relationships exist between the variables, but that these relationships change and vary across levels of the predictor variables. For aim 5, mediation analyses using ordinary least squares revealed that stress (PSS), loneliness (UCLA-R) and sleep quality (PSQI) influence perceived cognitive function (FACT-Cog) indirectly through feelings of anxiety and fatigue (PROMIS Scales). Finally for aim 6, correlational analyses among cytokines (IL-6, TNF-α) and individual and predictor variables (age, education, months since chemotherapy, BMI, PROMIS Scales, PSS, UCLA-R, PSQI, ESS, IPAQ) were re-examined separately in those BCS who were categorized as "impaired" and those that were "unimpaired". These analyses revealed significant correlations between IL-6, TNF-α, FACT-Cog and Trails A and B in the impaired group but not in the unimpaired group.

Chapter 5

Chapter 5 presents a summary and discussion of the study findings including the sample description, research questions, broader research considerations, and study limitations. The chapter concludes with implications for healthcare practice, future research, and public health policy.

STUDY SUMMARY

One of the most distressing (Boykoff et al., 2009), feared (Ganz et al., 2013) and prevalent (Janelsins et al., 2014) long-term effects of treatment that breast cancer survivors (BCS) face are deficits in the cognitive domains of memory, attention, processing speed, and executive functioning (Janelsins et al., 2014; Wefel & Schagen, 2012). Cancer-related cognitive impairments (CRCI) in survivors can impede daily functioning and quality of life (Duijits et al., 2014) and have a profound negative impact on social functioning, occupational performance, and overall well-being (Nelson & Suls, 2013). The mechanisms underlying CRCI in BCS remain unclear, but it is most often attributed to the neurotoxic effects of chemotherapy (Janelsins et al., 2011; Saykin & Ahles, 2007; Vardy, 2009). Research suggests that elevated inflammation may result in CRCI during and after chemotherapy (Cheung et al., 2014; Ganz et al., 2013; Janelsins et al., 2012; Kesler et al., 2013; Pomykala et al., 2013). Even though some treatment related factors have been identified as risk factors for both inflammation and CRCI in BCS (Janelsins et al., 2012; Kesler & Blaney, 2016; Tsvetkov, 2016), these factors are largely not modifiable or unavoidable when faced with a breast cancer diagnosis. It is possible that other factors may contribute to persistent CRCI either directly or indirectly (through inflammatory mediators) such as stress (Aggarwal et al., 2014; Carlson et al., 2007), physical activity (Beavers et al., 2010; Bherer, 2013), social isolation (Cacioppo &

Hawkley, 2009; Yang et al., 2013), and sleep quality (Clevenger et al., 2012; Miller et al., 2009; Sprod et al., 2010). These modifiable factors have been associated with inflammation and cognitive function in similar populations but have not been simultaneously evaluated in BCS.

The purpose of this study was to identify modifiable psychosocial and behavioral factors that may contribute to cognitive function both directly and indirectly through inflammatory mediators in BCS (ages 21 to 65), six months to 10 years after chemotherapy. Kang et al.'s (2010) integrated biobehavioral model provided a framework for exploring the impact of modifiable factors on inflammation and cognitive function in BCS. After receiving approval from the University of Texas at Austin's Institutional Review Board, 75 BCS ages 21 to 65 who were six months to 10 years post completion of chemotherapy, with a history of non-metastatic, non-inflammatory breast cancer were enrolled in the study.

SAMPLE DESCRIPTION

Demographic Characteristics

The demographic characteristics of this sample are similar to other studies within the field of CRCI in BCS— 90% of participants were White, well educated, and financially stable (Ganz et al., 2013; Janelsins et al., 2016; Kesler et al., 2013). Although the incidence of breast cancer in the U.S. is higher in non-Hispanic White women (128 per 100,000) than non-Hispanic Black women (124 per 100,000), Hispanic women (91 per 100,000), and Asian women (88 per 100,000), Black women were underrepresented in this study ("Breast Cancer Facts", 2015). Over 88% of the sample was working full or part time. More than a third were either divorced or never married, and the mean age of participants was 49 years, relatively younger than the median age for breast cancer occurrence in the U.S, 61 years of age ("Breast Cancer Facts", 2016). Seventy-two percent had gone through menopause, either naturally or secondary to BC treatment.

Disease and Treatment Characteristics

Over 70% of the sample had a history of invasive ductal carcinoma breast cancer and 84% had estrogen receptor positive breast cancer. The disease and treatment history of this sample is reflective of national statistics ("Breast Cancer Facts", 2016) and similar research studies (Kesler et al., 2013; Lyon et al., 2016; Muscatell et al., 2016). The percentage of participants in this study that had human epithelial receptor 2 (HER2) positive type breast cancer, 37.5%, was much higher than the national average of 14%. HER2-positive breast cancers tend to grow faster and are more likely to spread and recur compared to HER2-negative breast cancers. This higher percentage is likely attributable to how young the sample was and the fact that HER2-positive type breast cancer is more common in younger breast cancer patients (Keegan et al., 2012).

Almost every participant in this study underwent surgery as one of their treatment modalities (98.7%), which is slightly higher than national statistics — 94% of patients with stage I or II breast cancer undergo surgery, only 72% of those with stage III or IV do. Over half the sample had received anthracycline-based chemotherapy (56%), which is comparable to a recent nationwide longitudinal study of CRCI in BCS with over 500 participants (Janelsins et al. 2016). On average, women in this study completed chemotherapy treatment three years earlier, which is similar to several other studies (Kesler et al., 2013; Muscatell et al., 2016) conducted with BCS following chemotherapy. Like many studies of BCS, the demographic characteristics reflect a fairly homogenous sample (that is not as diverse as the population); however, the disease characteristics are more reflective of the general population.

Cognitive Function

Perceived Function. The FACT-Cog was used to operationalize perceived cognitive functioning in this study. Lower scores on this instrument indicate greater cognitive difficulties. FACT-Cog scores for participants in this sample were lower than

those reported by other researchers (Cheung et al., 2015, Janelisins et al., 2016) but higher than another (Bray et al., 2016), suggesting that the perceived cognitive function of these women were comparable to other BCS. Janelsins et al. (2016) recently studied the FACT-Cog in a nationwide cohort of 581 participants, and reported much higher scores than this study, suggesting that women six-months post-chemotherapy reported better cognitive functioning than the women in this sample who averaged three years post-chemotherapy completion. Worse perceived cognitive functioning in this sample could be due to the fact that the cohort of women were younger than those in the aforementioned studies. Research supports that younger survivors report more severe emotional distress and decreased quality of life than older survivors (Howard-Anderson , Ganz, Bower, & Stanton, 2012), and that emotional factors such as depressive symptoms, anxiety, and fatigue are inter-related with perceived cognitive functioning (Pullens et al., 2010, Jenkins et al., 2006; Jansen, 2013). The findings from this study are consistent with these reported associations. In fact, Janelsins et al. (2016) found that younger age was predictive of worse scores on the FACT-Cog Perceived Cognitive Impairments subscale. The same group of researchers found that anxiety and depression were predictive of worse scores on the FACT-Cog (Janelsins et al. 2016), much like the findings in this study that anxiety and fatigue (PROMIS scales) explained a large amount of variance in perceived cognitive functioning (FACT-Cog). It is also possible that survivors at six-months are less aware of their cognitive functioning than survivors a few more years after chemotherapy completion because they are focusing on other, more prominent treatment-related symptoms.

Cognitive Performance. Participants' neuropsychological (NP) scores, after age and educational adjustments, indicated average to above average performance. When scores on each NP test were dichotomized into impaired or unimpaired based on clinical guidelines, approximately 20% of the sample was considered to have at least one "mild

cognitive impairment". These findings are consistent with others in the literature that have reported 17-75% of study samples having mild cognitive impairment on at least one cognitive domain (Ahles et al., 2012; Wefel & Schagen, 2012). Although, the International Cancer and Cognition Task Force recommends the tests used in this study, they also recommend that researchers add other tests to their batteries (Wefel et al., 2011). Therefore, it is possible that the small battery of NP tests used in this study did not capture all the impairments that may have been present in the sample and could explain why the percentage of women with a mild cognitive impairment fell on the lower end of the range reported in the literature.

Perception and Performance Discrepancies. In this study, there were no relationships between the FACT-Cog and any of the NP test scores. These findings are consistent with the large body of research that has found weak relationships or no relationships between self-reports of cognitive function and NP measures (Andreotti et al., 2016; Hutchinson et al., 2012; Janelsins et al., 2014; Jim et al., 2012; Nelson et al., 2012). Considering that the participants in this sample perceived that problems with their cognitive functioning did exist, yet only 20% of the sample displayed mild cognitive impairment according to the NP measures, this calls to question whether NP measures are adequately capturing cognitive function within this population.

Even though NP tests are the gold standard for evaluating cognitive function, their sensitivity for detecting dysfunction or subtle changes in performance have been called into question for some time (Andreotti et al., 2016; Nelson et al., 2012). The test batteries that are used to measure cognitive function in cancer survivors were originally designed to detect impairments caused by overt brain trauma, brain lesions, or degenerative diseases that are typically accompanied by severe impairments. The psychometric limitations of these tests have been acknowledged in the field and include ceiling effects, restrictive range of scores, and low sensitivity in samples with average scores (Andreotti

et al., 2016). Furthermore, scores on standardized tests can be impacted by many factors including true neurocognitive performance, practice effects, regression to the mean, random measurement error, and human error in testing and interpretation calling into question the validity and reliability of these tests in BCS populations (Andreotti et al., 2016). Taken together, these findings suggest that the NP battery used in this study may not have been sensitive enough to capture all the cognitive impairments present in the sample. Furthermore, the lack of relationship between perceived cognitive functioning and cognitive performance suggest that these two measures may be capturing differing, or complementary, aspects of the complex phenomenon of cognition.

Cytokines

Normal human circulating IL-6 concentrations are approximately 1 pg/mL, with slight variations for women throughout their menstrual cycle (Angstwurm, Gartner, and Ziegler-Heitbrock, 1997). Researchers have reported that TNF-α concentrations for healthy, lean women average 2.2 pg/ml and for otherwise healthy but obese women average 8.6 pg/ml (Tsukui et al., 2000). This sample was slightly higher that normal for IL-6 concentrations (2.25 pg/ml ± 1.8) and within the lean to obese range (5.91 ± 1.40 pg/ml) for healthy women when compared to the study by Tsukui et al. (2000). Both cytokines exhibited a narrow range and small standard deviations.

RELATIONSHIPS AMONG STUDY VARIABLES

Despite the logic and supporting evidence gathered from the literature and presented in Chapter 2, IL-6 and TNF-α did not have significant, linear relationships with any of the modifiable psychosocial or behavioral variables or with the cognitive outcomes evaluated within this sample as a whole.

Psychosocial, Behavioral, and Inflammatory Factors

Researchers have previously reported associations between IL-6 and TNF-α and stress (Antoni, 2013; Bower et al., 2007; Carlson et al., 2007; Crosswell et al., 2014; Han

et al., 2015), loneliness (Jaremka et al., 2013; Marucha et al., 2005; Muscatell et al., 2015), sleep quality (Clevenger et al., 2012; Sprod et al., 2010), and physical activity (Jones, 2013 et al.; Pakiz et al., 2011, Rogers, 2013). Unlike in previous studies (Jones, 2013; Pakiz et al., 2011, Rogers et al., 2014 Clevenger et al., 2012; Sprod et al., 2010), we found scant significant relationships between the IL-6 and TNF-α and the behavioral factors. Linear, quadratic, and cubic functions also did not adequately explain the nature of the relationships between the psychosocial and behavioral factors and IL-6 and TNF-α. Rather, in this study, these relationships exhibited complex and non-linear patterns. The only significant relationship found between predictor variables and inflammatory cytokines was between BMI and TNF-α— suggesting that as BMI increases, levels of TNF-α also increase, but this relationship was small (r = .26). A small positive relationship approached significance between total minutes of physical activity (IPAQ Total Act) and IL-6 suggesting that more minutes of activity is associated with higher levels of IL-6. This finding is inconsistent with the literature presented in Chapter 2 that supported a negative relationship between IL-6 and physical activity, but could be explained by the fact that IL-6 has both pro and anti-inflammatory properties (Hunter & Jones, 2015; Kesler et al., 2013).

It is possible that these non-linear patterns of relationships are attributable to methodological problems in this study, or that the true nature of these relationships are in fact complex, and non-linear. First, the study was not powered based on the associations between the predictor variables and cytokines. Other possible explanations are that the measurement error associated with self-report measures (PSS, UCLA-R, IPAQ, PSQI, ESS) was too large or that these measures did not adequately measure the phenomena of interest— perceived stress, perceived social isolation, physical activity, and sleep quality. Using the IPAQ to quantify physical activity proved to be problematic and the instrument did not "behave" well psychometrically. It was both difficult to administer and for

participants to complete. Perhaps other measures such as the global physical activity questionnaire would more adequately capture physical activity (Hartman et al., 2015; Marinac et al., 2015).

It is possible that the amount of time that passed between when participants completed the self-report instruments and when they had their blood drawn could explain the lack of relationships. The number of days between survey completion and in-person appointments ranged from 0 to 22, but the average amount of time was 2.75 days, and the median was 1 day. The relationships between number of days between survey completion and in person appointment and the cytokine concentrations were evaluated and no significant relationships were found.

It is also plausible that the relationships between the predictor variables and cytokines are in fact non-linear, that serum cytokine levels are too unstable, or that the cytokine concentrations were influenced by factors not measured in this study. We know that the inflammatory cascade in the human body is incredibly complex. In fact, some have proposed that Chaos Theory is the best model for understanding this system (Callard, George, & Stark, 1999). IL-6 and TNF-α are involved in many aspects of the innate and adaptive immune systems, and their concentrations influenced by many upstream and downstream factors such as other chemokines, circulating hormones, circadian rhythm, and receptor inhibition (Hunter & Jones, 2015). These factors were taken into account when designing this study and procedures put into place to attempt to control for them. For example, all blood draws were completed on participants within 4 hours of them waking; participants taking any medications that would interfere with their inflammatory response (e.g. oral steroids, metformin) were excluded; and participants that had any comorbidities that are known to impact inflammation (e.g. autoimmune conditions, diabetes mellitus, unmanaged sleep apnea) were excluded. To ensure that time since waking in the morning did not influence cytokine concentrations, Pearson's

correlations were run between number of hours after waking in the morning and cytokines concentration, and no significant relationships were found. Recent research suggests that peripheral cytokines are "noisy" measures of inflammation, and genetic markers of pro-inflammatory expression, such as NF-kB, might be more robust and stable measures of inflammatory dysregulation (Creswell et al., 2012). It could be that genetic markers of inflammation, such as single nucleotide polymorphisms (SNPs), may be more stable over time, less sensitive to influence, and may be more robust biobehavioral measures (Doong et al., 2015). Genetic markers of inflammation should be considered as biomarkers in future studies incorporating inflammation in the conceptual model.

Inflammatory Factors and Cognitive Outcomes

No significant correlations were found between the cytokines (IL-6, TNF-α), perceived cognitive functioning (FACT-Cog total and subscales), and cognitive performance (HVLT-I scores, HVLT-D scores, COWAT scores, Trails A scores, Trails B scores). Scatterplots between all of these relationships revealed non-linear relationships even after data were transformed and variables median centered. These results are inconsistent with the literature supporting relationships between cytokines and cognitive outcomes in BCS (Cheung et al., 2015; Ganz et al., 2013; Kesler et al., 2013; Pomykala et al., 2013), but do support some findings from other studies (Booth et al., 2006; Janelsins et al., 2012). The lack of relationships between these specific cytokines and cognitive outcomes could be attributed to several factors— too much variability in length of time from chemotherapy completion for participants, lack of variability in cognitive performance measures, or not enough variability in cytokine concentration levels as discussed above.

This study included BCS from six months to 10 years after chemotherapy completion time, which bolsters external validity but hinders internal validity. It is possible that inflammation plays a role in cognitive functioning, but only at certain time

points throughout the survivorship trajectory. In one study, researchers have reported that six different cytokines varied in concentrations and associations with measures of cognitive performance in BCS as a function of time throughout a two-year period of time (Lyon et al., 2016). They specifically reported changes with IL-6 while participants were undergoing chemotherapy, and up to one year following treatment. Therefore, the PI ran an ANCOVA to look at group differences in cytokine concentrations by time since chemotherapy with IL-6 as dependent variable, then with TNF-α as the dependent variable, controlling for cancer stage. The five groups were Group One (six months to one year, n=13), Group Two (one to two years, n=14), Group Three (two to four years, n=23), Group Four (four to six years, n=10), and Group Five (six to 10 years, n=6). No significant group differences were found in cytokine concentrations. It is unlikely that time since chemotherapy can explain the lack of association between cytokines and cognitive performance in this sample.

It is also plausible that the study was underpowered to detect existing relationships. The original power analysis a medium-large effect size with f^2=0.21, two-tailed α = .05, power of .80, and five predictors yielded 68 participants. Blood could only be obtained from 66 of the participants resulting in only 66 participants included in analyses for aims 1 & 2. Although the study was underpowered, it is unlikely that two additional participants would have impacted the magnitude and significance of the Pearson's correlations reported in Table. 4.4, which ranged from .04 to .17.

The findings could also be explained by lack of variability in neurocognitive functioning within this group of women who overall exhibited average to above-average performance (as seen in the box plots in Figures 4.3-4.5). Even though cognitive performance was fairly homogenous in the sample, anecdotally, the vast majority of the sample reported cognitive problems to the PI during the data collection meetings. It is possible that the sensitivity of IL-6 and TNF-α to cognitive performance is only

detectible when there is a larger range of performance scores that include lower performance scores (Patel et al., 2015). Similarly, there was not a large range in cytokine concentrations themselves, and it is possible that there was not enough variability to detect linear relationships. The levels of IL-6 were on average 2.25 pg/ml (SD 1.80). These levels were closer to those in the control group than to the breast cancer patient group in another study (1.84, SD 1.21; Patel et al., 2015). These researchers reported significant relationships between cytokines (IL-6 and sTNF-RII) and memory performance in the breast cancer group, which had higher levels and more variability than the control group (Patel et al., 2015). It is possible that a linear relationship exists between the cytokines and cognitive performance at higher concentrations of IL-6 and TNF-α that were not captured in this sample. Furthermore, this study only evaluated a limited number of both cognitive tests and cytokines, and a more comprehensive evaluation, including more tests and larger panels of cytokines might be needed in order to understand the mechanistic role that inflammation plays in the cognitive functioning of BCS.

Psychosocial and Behavioral Predictors of Cognitive Outcomes

Several overall patterns of correlations were identified in this study between individual factors, psychosocial and behavioral factors, perceived cognitive function, and cognitive performance. As expected, age and years of education were significantly related to cognitive performance measures, but not perceived cognitive function. Only BMI was significantly related to perceived cognitive function, which is inconsistent with other reports of BMI having no relationship with FACT-Cog scores in BCS (Myers et al. 2017). Moderate to large relationships were found between all of the psychosocial and sleep variables and perceived cognitive function, suggesting that higher levels of emotional distress (PROMIS Anxiety, PROMIS Depression), fatigue (PROMIS Fatigue), stress (PSS) and loneliness (UCLA-R) are related to worse perceived cognitive

functioning (FACT-Cog). These findings are consistent with the literature (Ottati et al., 2013; Li et al., 2014; Mehlsen et al., 2009; Myers et al., 2015; Jaremka et al., 2014). Surprisingly, there were no significant relationships between physical activity measures and perceived cognitive functioning, which is contrary to recent findings that self-reported exercise was significantly related to FACT-Cog (Myers et al., 2017). This inconsistency may be attributed to how Myers et al. (2017) measured self-reported exercise—one question asking participants how often they exercised in the past month with four answer choices.

Only two significant relationships were found between the psychosocial and behavioral factors and the cognitive performance measures in this study, suggesting that as sleep quality worsened (PSQI) so did delayed memory performance (HVLT-D), and as number of active minutes per week increases (IPAQ Act Min), executive functioning worsens (Trails B), an unexpected finding. These findings are contrary to other studies that found associations between self-reported exercise and cognitive performance measures (Hartman et al., 2015; Pradhan et al., 2015). These differences in findings could be attributed to the use of a different instruments to capture physical activity and the other studies were likely powered adequately to detect the relationships between lifestyle factors and cognitive performance (Hartman et al., 2015; Pradhan et al., 2015).

AIM 1: TO ASSESS THE IMPACT OF PSYCHOSOCIAL (STRESS, SOCIAL ISOLATION) AND BEHAVIORAL (PHYSICAL ACTIVITY, SLEEP QUALITY) FACTORS ON INFLAMMATORY MARKERS (IL-6, TNF-A) AFTER CONTROLLING FOR SELECTED INDIVIDUAL FACTORS.

This study provides a unique contribution to the literature by illustrating the non-linear relationships between the selected psychosocial and behavioral variables and cytokines. It was determined that the assumption of linearity was violated in the preliminary analyses, therefore curvilinear (cubic) simple regression models were used to determine the variance of cytokines (IL-6 and TNF-α) explained by the predictor

variables. No studies were identified in the literature describing curvilinear relationships between the psychosocial and behavioral variables in this study and either IL-6 or TNF-α. Of all the predictors, only daytime sleepiness (ESS) was a significant predictor of IL-6 concentrations. The cubic regression line in this model had two "bends" and explained 11% of the variance. It is well established that daytime sleepiness associated with sleep disorders like sleep apnea and narcolepsy is associated with higher levels of IL-6, but the link has not yet been made in BCS.

No relationships were found between IL-6 and loneliness which is inconsistent with the research from Hughes et al. (2014), who reported that loneliness predicted IL-6 concentrations in BCS using a standard linear regression ($b = -.009$, $t(87) = -2.12$, $p = .037$, R^2 change = .02). This discrepancy could be explained by their large sample (N=164; Hughes et al., 2014). Our findings are consistent with Muscatell et al. (2016) that reported no significant relationships between loneliness and IL-6 ($r = -.37$, $p = .18$, n=15). No significant predictors were found using the curvilinear (cubic) simple regression models with TNF- α as the dependent variable.

AIM 2: TO ASSESS THE IMPACT OF INFLAMMATORY MARKERS (IL-6, TNF-A, IL-6* TNF-A) ON COGNITIVE FUNCTION (COGNITIVE PERFORMANCE, PERCEIVED COGNITIVE FUNCTIONING) AFTER CONTROLLING FOR SELECTED INDIVIDUAL FACTORS.

The findings related to this aim are contrary to the growing body of research supporting linear relationships between cytokines and cognitive function in BCS who have undergone chemotherapy (Ganz et al., 2013; Janelsins et al., 2012; Kesler et al., 2013; Patel et al., 2015; Muscatell et al., 2016). It was determined that the assumption of linearity was violated between cytokine concentrations and cognitive measures in the preliminary analyses; therefore, curvilinear (cubic) simple regression models were used to determine the variance in cognitive outcomes that was explained by the cytokines. The PI found no reports in the literature of curvilinear modeling between these variables in

BCS populations. These findings provide unique knowledge about the complex relationships that exist between IL-6, TNF-α and cognitive measures in BCS. Only one significant cubic predictor was identified in all of these regression models. TNF-α significantly explained 2.7% variance in delayed memory performance (HVLT-D). These findings are inconsistent with a recent study by Lyon et al. (2016) that described linear relationships between cytokines and cognitive performance across time starting before chemotherapy and continuing two years after chemotherapy ended. These researchers report that the relationships between cytokine concentrations and cognitive measures varied across time, suggesting that the relationships between IL-6, TNF-α, and cognitive performance could be curvilinear when evaluated cross-sectionally in a group of BCS from six months to 10 years following chemotherapy (Lyon et al., 2016).

AIM 3: TO EXPLORE DIRECT AND INDIRECT EFFECTS (THROUGH INFLAMMATORY MEDIATORS IL-6 AND TNF-A) OF PSYCHOSOCIAL (STRESS, SOCIAL ISOLATION) AND BEHAVIORAL (PHYSICAL ACTIVITY, SLEEP QUALITY) FACTORS ON COGNITIVE FUNCTION (MEMORY, ATTENTION, PROCESSING SPEED, EXECUTIVE FUNCTION PERFORMANCE, PERCEIVED COGNITIVE FUNCTION) AFTER CONTROLLING FOR SELECTED INDIVIDUAL FACTORS.

The findings related to this aim indicated that perceived cognitive function is not only explained by emotional distress (Asher, 2011; Poppelreuter et al., 2004; Pullens, De Vries, & Roukema, 2010) and fatigue (Bower & Lamkin, 2013; Cheung et al., 2013; Hodgson et al., 2013; Hutchinson, et al., 2012), but that stress, loneliness, and sleep quality can also influence perceived cognitive functioning in BCS. The analyses for aim 3 focused on exploring the direct effects of psychosocial and behavioral predictors on cognitive function because the relationships between the majority of the predictors and cognitive outcomes were linear. The findings from the hierarchical regression analyses suggest that anxiety (PROMIS Anxiety) and fatigue (PROMIS Fatigue) but not

depressive symptoms (PROMIS Depression), are related to perceived cognitive function (FACT-Cog). These findings support those reported by Li et al. (2015) that hyper-arousal and fatigue, *together* explained 26% of the variance in perceived cognitive impairments in BCS. The findings are consistent with the literature linking self-report emotional and psychosocial measures with self-report measures of cognitive function in BCS (Cheung et al., 2015; Janelsins et al., 2016; Myers et al., 2015; Myers et al., 2017).

Controlling for age and years of education, daytime sleepiness (ESS), perceived sleep quality (PSQI), and minutes of physical inactivity (IPAQ Min Sit) significantly explained 9.1% of the variance in delayed verbal memory performance (HVLT-D). It appears that perceived sleep quality (PSQI scores) accounted for the majority of this variance explained. Links have been made between objectively measured sleep in older adults but not between perceived sleep quality (PSQI scores) and HVLT scores (Cavuoto, 2016), suggesting that objectively and subjectively measures sleep quality are measuring different aspects of sleep quality. These findings support those by other researchers that describe inconsistent relationships between sleep parameters and cognitive outcomes (Brewster et al., 2015). When controlling for age, use of a sleep aid (PSQI Sleep aid Subscale) and minutes of physical activity (IPAQ Min Act) significantly explained 7.6% of the variance in the measure of executive functioning (Trails B scores) and it appears that minutes of physical activity (IPAQ Min Act) accounted for the majority of this explained variance. These results support the findings of other studies (Miki et al., 2014; Pradhan et al., 2014; Pradhan et al., 2016) and extend the findings of Crowgey et al. (2014) who reported significant relationships between self-reported exercise and verbal memory. Additionally, these study findings could be spurious due to multiple comparisons and uncorrected p values in the analyses.

ADDITIONAL ANALYSES

The findings from aims 1 and 2 suggested that the associations among the psychosocial, behavioral factors, and cytokines, and between the cytokines and cognitive outcomes were not linear, quadratic, or cubic. Therefore, non-parametric procedures were utilized to adequately describe the extant relationships among these variables in aim 4. Furthermore the results from aim 3 showed significant inter-correlations between the psychosocial variables, sleep quality, and perceived cognitive function, so the direct and indirect effects of psychosocial factors (stress, perceived social isolation, emotional distress, and fatigue) and sleep on perceived cognitive function were explored. Finally, research suggests that relationships between peripheral cytokines and behavioral factors may only emerge within populations in pathological states; therefore, the patterns of correlations between individual factors, predictor variables, and cytokines were explored in participants categorized as cognitively "impaired" and those categorized as "unimpaired" in aim 6.

Aim 4: To describe the nature of the relationships between psychosocial and behavioral factors and cytokines, and between cytokines and cognitive outcomes.

Loess modeling techniques were used to extend understanding of the complex relationships that exist between psychosocial, behavioral, and cognitive variables and IL-6 and TNF-α. As part of the analyses for aims 1 and 2, cubic functions were used to fit the data with cytokines either as the predictor or the dependent variables. These models fit the data better than linear and quadratic models, but the curvilinear regression analyses proved that they were still not "great models" to explain the true nature of the relationships. Loess modeling was used to explore the complexities of these relationships and illustrated many bends in the regression lines that changed and varied across levels of the predictor variables. Similarly, when the cognitive outcomes were regressed on the cytokine variables using Loess lines of best fit, these graphs showed linear relationships

do exist between the variables but only at certain levels of cytokines. These relationships appear very steep and strong at certain levels of the cytokine variables. Only graphs between IL-6 and immediate verbal memory (HVLT-I) and TNF-α and executive functioning (Trails A and B) were essentially straight across all levels of the cytokines suggesting either too much "noise" error in the data collected, or no relationship exists between the variables. To the PI's knowledge, this is the first study to analyze and report Loess regression plots describing the complex nature of relationships between cytokines and psychosocial, behavioral, and cognitive variables in BCS.

Aim 5: To explore direct and indirect effects of psychosocial factors (stress, perceived social isolation, emotional distress, and fatigue), and sleep quality on perceived cognitive function.

The results of the study support that feeling more stress, social isolation, and experiencing worse sleep quality may result in poorer perception of cognitive functioning in BCS and that these effects are likely mediated by feelings of anxiety and fatigue. Pearson's correlation analyses showed moderate to large correlations between the psychosocial variables (PROMIS Scales, PSS, UCLA-R), sleep quality (PSQI) and perceived cognitive function (FACT-Cog). There were significant relationships between the psychosocial and sleep variables as well. Therefore, a two-step hierarchical regression analysis was run and the results of this analysis revealed that only anxiety (PROMIS Anxiety) and fatigue (PROMIS Fatigue) remained significant predictors of perceived cognitive function (FACT-Cog), but that perceived stress (PSS) approached significance. These results suggested that perceived stress (PSS), loneliness (UCLA-R), and sleep (PSQI) impact perceived cognitive function (FACT-Cog) through indirect pathways of anxiety (PROMIS Anxiety) and fatigue (PROMIS Fatigue); therefore, a mediation analysis was conducted using ordinary least squares to explore the pathway. The findings of the mediation analysis are consistent with those found in the literature linking

psychosocial and emotional factors to perceived cognitive function and extend our knowledge of *how* these factors may impact perceived cognitive function. Specifically, 1) perceived stress (PSS) may impact perceived cognitive function (FACT-Cog) both directly and indirectly through perceived anxiety and feelings of fatigue (PROMIS Scales); 2) loneliness (UCLA-R) may only indirectly effect perceived cognitive function (FACT-Cog) through anxiety and fatigue (PROMIS Scales), and 3) sleep quality (PSQI) may only indirectly effect perceived cognitive function (FACT-Cog) through anxiety and fatigue (PROMIS Scales). There is scant research on the nuances of how emotional distress, stress, loneliness, and sleep quality are related to perceived cognitive function. Our findings are consistent with Reid-Arndt (2011) who reported that helplessness mediates the relationship between self-reported stress and cognitive functioning ($p<.01$) in BCS.

Aim 6: To explore patterns of relationships between cytokines (IL-6, TNF- α) and cognitive measures (FACT-Cog, HVLT-I, HVLT-D, COWAT, Trails A, Trails B) in BCS classified with "mild cognitive impairment" and those classified as "unimpaired".

The range for healthy levels of cytokines is very narrow, so it is possible that the relationships between cytokines and cognitive function are only detectable when cytokines are outside of this window, in pathological states (i.e. cognitively impaired individuals), and the range is wider. Similar patterns of relationships have been reported in the field of persistent fatigue in BCS— significant relationships between peripheral cytokines and behavioral factors in fatigued BCS but not in non-fatigued survivors (Bower & Lamkin, 2013). To explore whether patterns of correlations differed by cognitive impairment status, the sample was divided into impaired (n=13, -1.5 SD below the mean on at least one NP test) and unimpaired individuals (n=53).

The patterns of correlations were in fact different between groups. In the impaired group, significant large *negative* relationships were observed between perceived

cognitive function (FACT-Cog) and both IL-6 and the interaction between IL-6 and TNF-α, and in the unimpaired group, a moderate *positive* relationship was observed between TNF-α and perceived cognitive function (FACT-Cog). In the impaired group moderate positive relationships were observed between the measures of attention and executive function performance (Trails A and B) and the interaction of IL-6 and TNF-α and between just the Trails B scores and TNF-α. No significant relationships were found between the cytokines and NP test scores in the unimpaired group.

These findings suggest that there may be significant linear relationships between perceived cognitive function (FACT-Cog), executive functioning performance (Trails A and B), and the cytokines (IL-6 and TNF-α) in those BCS who have mild cognitive impairment. More specifically, as levels of IL-6 increase, perceived cognitive functioning (FACT-Cog) worsens; as levels of TNF-α increase, executive functioning worsens (Trails B); and that the interaction between IL-6 and TNF-α (but not individual concentrations of either cytokine) is related to attention (Trails A). Interestingly, the only significant relationship found in the unimpaired group was a moderate positive relationship between perceived cognitive function (FACT-Cog) and TNF-α, which was in the opposite direction of the relationships in the impaired group.

Differing patterns of correlations were also observed in the impaired and unimpaired groups between the cytokines (IL-6, TNF-α) and individual and predictor variables (age, education, months since chemotherapy, BMI, PROMIS Scales, PSS, UCLA-R, PSQI, ESS, IPAQ). A significant positive relationship was found between BMI and IL-6 and the interaction term in the impaired group, suggesting that as BMI increases so does IL-6 in this group. The opposite pattern was observed in the unimpaired group suggesting that as BMI decreases in the unimpaired group, IL-6 levels increase. For the predictor variables, a large positive relationship was observed between daytime sleepiness (ESS) and IL-6 and the interaction term suggesting that as daytime sleepiness

worsens, IL-6 levels increase in the impaired group. Again, the opposite pattern was observed in the unimpaired group suggesting that as daytime sleepiness worsens, IL-6 levels decrease.

Taken together, these exploratory findings suggest that the patterns of relationships between cytokines, daytime sleepiness, BMI, perceived cognitive function, and executive functioning are different for those BCS with cognitive impairments than for those BCS without cognitive impairments. These exploratory correlation analyses in the impaired and unimpaired groups help explain the curvilinear relationships found in the Loess regression modeling. Importantly, the sample of impaired BCS was very small, requiring non-parametric correlation analyses (n=13) and the findings need to be replicated in a larger sample of BCS with "mild cognitive impairment" in order to draw conclusions. Additionally, the p values in these analyses were not adjusted for multiple comparisons, therefore, type I error was inflated and it is possible that the significant correlations are due to chance.

CONCEPTUAL MODEL

The biobehavioral model (Kang et al., 2010), used in this study provided a useful conceptual approach to understanding how psychosocial, behavioral, and biological factors are related to and influence CRCI in BCS following chemotherapy. In the present study, it was theorized that psychosocial, behavioral, and biological factors would influence CRCI through direct and indirect pathways. Kang et al. (2010) explain that these pathways are complex, and may be bi-directional. Using this conceptual model shed light on how psychosocial predictors impact perceived cognitive function but not cognitive performance.

Considering inflammation was a central factor in the conceptual model, and that the pro-inflammatory cytokines chosen to test in this model did not explain variability in BCS' cognitive function, it calls to question whether the model should be refined.

Perceived stress, emotional distress, fatigue, loneliness, and sleep quality did in fact predict perceived cognitive function, and it is possible that other biological measures of inflammation might explain how the modifiable factors in this study influence CRCI (Wang et al., 2015; Wardill et al., 2016). In this study, cognitive function was operationalized in two ways— perceived cognitive functioning and neuropsychological performance. This model proved useful in understanding the nuances of perceived cognitive function but not cognitive performance. This supports the notion that perception and performance are different phenomena and that different mechanisms may be responsible for the development and persistence of each.

In future studies, the model could be refined in a way to better operationalize the "biological factor" of inflammatory dysregulation. The decision to use these two pro-inflammatory cytokines, IL-6 and TNF-α, was based on the most recent findings at the time of the study inception and design (Ganz et al., 2013, Pomykala et al., 2013, Kesler et al., 2013, Cheung et al., 2014, Janelsins et al., 2012). In the last three years, the science has evolved, and supports the likelihood that other cytokines play a role in the dysregulation (Lyon et al., 2016; Wang et al., 2015; Wardill et al., 2016) and that peripheral cytokine data is in general is "noisy" and unreliable (Creswell et al., 2012). Although IL-6 has been discussed as a "prototypical pro-inflammatory" cytokine in BCS research, Lyon et al. (2016) suggest that other cytokines "may be key to understanding the neuro-inflammatory connection in BCS", such as IL-17 or IL-10 that correlated with several cognitive domains at various times in the treatment and recovery trajectory in their study (p 79). It is possible that cytokines are not the ideal measure for "inflammatory dysregulation" and more stable biomarkers such as genomic markers of inflammatory up-regulation, such as NF-kB, should be used to capture the phenomena. Another group of researchers recently reported that the SNP, IL1R1rs2287047, was significant predictor of perceived cognitive function in BCS (Myers et al., 2017).

STUDY LIMITATIONS

There were limitations to this study. First, the findings can only be generalized to women with a history of non-metastatic, non-inflammatory breast cancer who received chemotherapy as part of their treatment regimen. Even though efforts were made to recruit a diverse sample for the study, the majority of the sample was White, well educated and financially stable; therefore, the external validity is limited demographically. Second, as in all studies, the measures in this study were subject to bias and error. The majority of the instruments in this study were self-report and that data could have been influenced by recall bias (participants may have difficulty remembering or inaccurately report data). The neurocognitive tests used in this study could have been impacted by ceiling effects, regression to the mean, random measurement error, and human error in testing and interpretation, calling into question their validity and reliability (Andreotti et al., 2016). Furthermore, only four neuropsychological tests were administered, limiting the assessment of "cognitive performance". The study did not have either a non-chemotherapy or non-breast cancer comparison group, which limits the interpretations of the findings. The study was limited by sampling bias because only motivated women willing to travel for the study were included, the findings cannot generalize to women who could not attend or did not have the resources to participate. Finally, this study was cross-sectional; therefore, causality cannot be assumed.

The biomarkers chosen for this study may not have adequately captured the phenomena of inflammatory dysregulation related to CRCI in BCS. Many factors could have increased the "noise" of this data including difficulty obtaining blood samples (i.e. breast cancer survivors are typically limited to blood draws in one arm secondary to lymph node removal, "chemo-veins"), damage to the samples during processing, potential damage to materials used for blood sampling, human error in running ELISA analysis, and cytometry machine error. The cytokine panel could either be expanded to

include many circulating cytokines or replaced by a genetic marker of pro-inflammatory expression. The surveys could be administered during the in-person appointments to limit the number of "life events" that could occur between the survey and the other data collected. Also, a biomarker obtained from saliva measurement might be better choice since saliva samples are easier to collect, and could be collected from participants living in other parts of the country through the mail. A clinical marker of peripheral inflammation such as C-reactive protein could be included since this measure is already monitored regularly in oncology settings.

The following methodological changes could be made to address these limitations. To address the limitations in measurement, a different measure of physical activity could be used such as the global physical activity questionnaire (Hartman et al., 2015) or accelerometers (Marinac et al., 2016). The cognitive test battery could be modified to use the Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 2012) instead of the HVLT-R and the Comprehensive Trail Making Test (CTMT; Moses, 2004) instead of the Trails A & B, both of which require more cognitive demands and would likely result in a greater range and variability in performance. Alternatively, neuroimaging could be used in place of NP testing to quantify cognitive performance. Since different patterns of correlations were seen in those BCS who were classified with mild cognitive impairment than those classified as unimpaired, a larger and more homogenous group of impaired BCS should be recruited to further evaluate these relationships. This could be accomplished by adding a NP test to the prescreening tool. A larger more homogenous sample of BCS who have mild cognitive impairment would allow for a better a more comprehensive understanding of the relationships among the predictor variables, cytokines, and cognitive outcomes in this population.

IMPLICATIONS FOR CLINICAL PRACTICE, FUTURE RESEARCH, AND PUBLIC POLICY

Clinical Practice

Some BCS perceive cognitive dysfunction for up to 10 years following the end of their chemotherapy. Even though in this study the majority of the survivors' cognitive performance on NP tests fell into the average to above average range, approximately 20% were classified with "mild cognitive impairment" on at least one NP test. The study findings suggest that this group as a whole still perceive problems with their cognitive functioning when asked about their day to day lives, and that these perceptions are unrelated to their performance on NP tests. Healthcare providers are in a position to support BCS after treatment is over. Providers must acknowledge survivors' concerns and assess cognitive functioning throughout the cancer trajectory. It is essential that providers acknowledge that cancer-related cognitive changes may be influenced by many factors that extend far beyond receiving chemotherapy. The findings from this study highlight the importance of assessing and managing emotional distress, psychosocial needs, and sleep quality throughout survivorship. Patient reported outcomes are gaining traction in both clinical and research settings. The PROMIS scales are available free of cost and provide psychometrically sound tools for clinicians and researchers to use to measure symptoms such as anxiety, depression, fatigue, perceived cognitive impairments, and sleep quality. Most of the scales are eight items or less and are easy to administer and score (http://www.healthmeasures.net/resource-center/nih-toolbox-ipad-app).

Treatment history alone did not explain variations in cognitive functioning in this group of women, suggesting that other factors besides treatment may be influencing cognitive functioning. Healthcare providers must look beyond cancer treatments and consider lifestyle modifications when assessing and managing cognitive dysfunction in survivors including improving sleep quality, managing stress, increasing physical activity. When providers are considering recommendations for patients reporting

cognitive problems, it is important to consider that psychosocial interventions may be beneficial for improving perceived cognitive functioning in addition to those targeted at increasing physical activity or teaching compensatory strategies. If time is a limited resource for a particular patient, suggesting stress management and relaxation therapies might be the best choice for patients complaining of CRCI, based on the findings from this study. Mind-body therapies may be appropriate interventions for survivors experiencing emotional distress, stress, or cognitive dysfunction especially if inflammatory mechanisms are playing a role in symptomology. Recent research suggests that mind-body therapies may improve regulation of inflammatory pathways in the body (Morgan et al. 2014; Bower & Irwin, 2016). Bower et al. (2015) conducted a pilot study with premenopausal BCS utilizing a mindfulness intervention and reported significant reductions in perceived stress, pro-inflammatory gene expression, and inflammatory signaling.

Future Research

The findings from this study prompt further inquiry in the field of CRCI. Directions for future research include:

1. The study findings support that more stress, social isolation, and sleep quality impact perceived cognitive functioning in BCS. Importantly, the constructs of stress and social isolation are very complex and a more in depth evaluation of the concepts within each of these constructs is needed. For example, when considering stress, one should also consider the concept of "coping". Researchers have started to look at the impact of stress and coping in BCS (Reid-Arndt & Cox, 2012) and have started to theorize the role of self-regulatory capacity in regards to stress in BCS (Arndt et al., 2014). Reid-Arndt & Cox (2012) reported that passive coping styles mediated the negative effects of perceived stress on cognitive functioning in their sample. Their sample was small (N=36) and more research is needed to replicate these findings in other samples and to understand how

emotional factors fit into the model of stress, coping, and perceived cognitive functioning.

Similarly, loneliness should not be considered in conceptual isolation. Other concepts such as social support, social environments (Cacioppo & Hawkley, 2009), and personality traits should be considered. Weiss (1973) theorized that the experience of loneliness involves both social and emotional components. The results from this study support Weiss' theory in that loneliness impacted cognitive function indirectly through emotional feelings of anxiety and fatigue. Hawkley and Cacioppo (2010) proposed a Loneliness Model that explains how loneliness can impact cognitive functioning starting with feelings of being unsafe that result in a hyper-vigilance and subsequently result in cognitive biases that lead to negative social experiences. This model has yet to be applied to the study of CRCI in BCS and could be useful in future studies aimed to better understand the mechanisms of loneliness and cognitive function in BCS.

2. The results from this study suggest that the NP tests recommended to use in this population may not be sensitive enough to detect the cognitive dysfunctions that BCS experience (Wefel & Vardy, 2011). Considering that only 20% of the participants exhibited mild cognitive impairment (-1.5 SD or more below the age and education adjusted mean scores) on one or more of the cognitive tests, calls to question whether the NP tests recommended by the ICCTF in 2011 to evaluate BCS' cognitive performance are sufficient measures for quantification of CRCI (Wefel & Vardy, 2011). Perhaps other NP tests would be more sensitive to the cognitive deficits in this population such as the Comprehensive Trail Making Test (CTMT; Moses, 2004) and the Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 2012). The Trails A and Trails B that were used in this study are part of the CTMT but the CTMT has three additional tests that are more complex and require more executive resources including executive attention and control and working memory. The HVLT-R used in this study is similar to the RAVLT, but the

RAVLT is more complex as there are 16 words rather than 12 to recall over multiple trials, challenging short and long-term memory more than the HVLT-R. Research also supports that brain imaging data is more sensitive to structural and functional changes reported by BCS, and is more often associated with perceived functioning (Kesler et al., 2017, Muscatell et al., 2016); therefore, neuroimaging may be a preferred way of objectively quantifying CRCI in BCS.

3. The follow up analyses looking at the correlations separately in the impaired group of BCS and those that were unimpaired indicated that the relationships between cytokines and cognitive measures are very different. Future research should evaluate the variables in this study using the biobehavioral model (Kang et al., 2010) in sample of BCS with more serious cognitive impairment to better understand how these variables are related to and interact to affect cognitive performance in BCS.

4. There is a need to better understand the impact of hormonal therapies on cognitive function in survivors following chemotherapy because the majority of survivors will be on these treatments for 5-10 years. A link has already been made between tamoxifen use and worse cognitive functioning in BCS (Janelsins et al., 2012; Jim et al., 2012; Schilder et al., 2009), but how hormonal therapies interfere with the neuroendocrine systems in BCS is poorly understood at this time. Most survivors will go on and off various endocrine treatments throughout the survivorship phase and it is likely that these personalized treatment regimens interfere with cognitive functioning, but we do not know exactly how at this time. Fortunately, a research group out of the Netherlands is starting to address these research questions (Zwart et al., 2015).

5. The vast majority of CRCI research has been conducted with BCS, including the present study. Research needs to expand to include the experiences of persons with other types of cancer. Evidence supports cognitive changes in testicular, colon, and prostate cancer survivors but little research has been done in these areas (Gunlusoy et al.,

2017; Harrington et al., 2010; Stouten-Kemperman, 2015). A recent review of CRCI in hematological cancers concluded that, "The limited CRCI literature in hematological malignancy survivors is currently dominated by studies of childhood acute lymphoblastic leukemia survivors" (Williams et al., 2015, pp. 843), so work in the area of adult hematological survivors is also needed.

Additionally, there is a need to expand the age criteria of studies of CRCI to include older survivors who are typically excluded from studies, despite the fact that breast cancer is more prevalent in older women. Very few studies have focused on CRCI in older survivors (Loh et al., 2016; Mandelblatt et al., 2013; Mandelblatt et al., 2015) highlighting the need to study this phenomenon in women over age 65. Similarly, women with metastatic breast cancer are often excluded from CRCI related studies. Now that women with stage IV breast cancer are living longer with their disease, a better understanding of their cognitive functioning throughout their treatment is essential.

6. Since the Loess Regression plots illustrated that the relationships between cytokines and cognitive measures in this study were complex, a multivariate non-linear, analysis of the data using Random Forest Regression (Breiman, 2001) should be conducted to understand the best model to fit the data and to determine an algorithm to predict cognitive function with the psychosocial and inflammatory factors. Random Forest Regression is a non-parametric type of machine learning that analyzes all possible interactions that could occur between the predictor variables and the dependent variable utilizing bootstrapping sampling of training sets. Predictor variables are chosen based on prior knowledge from the literature and thus allow for hypothesis testing. Random Forest Regression is robust to "model over fitting", and an appropriate choice when the sample size is small or there are a large number of predictors (Breiman, 2001).

7. Another consideration for future research is that the FACT-Cog is a 37-item questionnaire and two shorter surveys have been developed directly from this measure

and are available in the NIH PROMIS toolbox. The PROMIS Cognitive Abilities, and PROMIS Cognitive Impairments Scales are both eight items long and are psychometrically sound. Using shorter scales could decrease study burden on participants, especially those who are cognitively fatigued, anxious, or feeling depressed (http://www.healthmeasures.net/resource-center/nih-toolbox-ipad-app).

8. Considering the relationships found between sleep quality (PSQI) and daytime sleepiness (ESS) and both inflammation and cognitive functioning, a secondary analysis of the data focusing on sleep as the primary variable is warranted. Historically, people who score greater than five on the PSQI have been classified as "poor sleepers". Therefore, analyses could be conducted to explore group differences in cytokine concentrations and cognitive outcomes between poor sleepers and good sleepers.

Public Policy

Approximately 3.1 million women have survived breast cancer in the United States (DeSantis et al., 2014). CRCI is a devastating and pervasive problem within the BCS community. CRCI can lead to poor quality of life and difficulty functioning day to day. If policy makers prioritize improving the cognitive functioning of these women, it may lead to more independence and better quality of life. Funds for research must be allocated to focus on both the mechanisms behind this treatment-related burden and on effective treatments to mitigate CRCI. Additionally, adequate cognitive assessment and management need to be included in oncology standards of care. Nurses, physicians, and other providers need to be educated on the cognitive effects of cancer and cancer treatment and interventions to mitigate these symptoms. Insurance coverage is needed for adequate cognitive assessment (fMRI or NP Battery) for survivors who require comprehensive assessments. Health insurance should cover or subsidize the cost for interventions to improve emotional and cognitive functioning throughout and following cancer treatment. Fortunately, in 2009 the American's with Disabilities Act (ADA) was

amended to include and cover individuals who experience disabilities as a result of their cancer and prohibits discrimination of these individuals (https://www.eeoc.gov/laws/types/cancer.cfm). Policy makers need to ensure that the ADA is enforced and that those who are substantially limited in a major life activity either physically or cognitively, as a result of their cancer are adequately covered by the ADA.

CHAPTER SUMMARY

The purpose of this study was to identify modifiable psychosocial and behavioral factors that may contribute to cognitive function both directly and indirectly through inflammatory mediators in BCS six months to 10 years after chemotherapy. Contrary to expectations, IL-6 and TNF-α levels were unrelated to the modifiable predictor variables and did not predict either perceived cognitive functioning or cognitive performance in this sample as a whole. However, some correlations did emerge when the sample was divided into those BCS classified with "mild cognitive impairment" and those without impairment between IL-6, the interaction of IL-6 and TNF-α and perceived cognitive function (FACT-Cog); and between TNF-α, the interaction of IL-6 and TNF-α and executive functioning (measured by Trails A and B). The subsample of participants with impairments was very small (n=13) making it difficult to draw conclusions; so, these relationships need to be evaluated in a larger, more homogeneous sample of BCS experiencing cognitive impairment.

The state of the science in this field has evolved since the inception of this study and genetic biomarkers of pro-inflammatory dysregulation may be more stable and predictive of cognitive function. The findings from this study suggest that perceived stress and loneliness contribute to perceived cognitive functioning in breast cancer survivors but that elevated IL-6 and TNF-α do not mediate these effects. These findings may be reflective of methodological problems discussed above in the "Limitations"

section, or they may reflect the complex nature of relationships involving cytokines. Additional non-parametric analyses in this study illustrated that the cytokines were related to the predictor variables but that the relationships varied in direction and magnitude across levels of the predictor variables. Similarly, cognitive outcomes were related to the cytokines, but these relationships varied in direction and magnitude across levels of the cytokines. In three cases, the graphs suggested that no relationships existed between factors: 1) IL-6 and HVLT-I; 2) TNF- α and Trails A, and 3) TNF- α and Trails B.

When evaluating the direct effects of the predictor variables on cognitive function, two patterns emerged from the data. Psychosocial variables (perceived stress, loneliness, anxiety, and fatigue) and sleep quality predicted perceived cognitive function, and behavioral factors (physical activity, sleep quality) predicted verbal memory and executive functioning performance. The effects of psychosocial variables on perceived cognitive function were examined further. Effects of feeling more stress, social isolation, and experiencing worse sleep quality on cognitive functioning were mediated by feelings of anxiety and fatigue.

CONCLUSION

Cognitive dysfunction following breast cancer treatment is a serious and pervasive problem (Janelsins et al., 2017; Janelsins et al., 2014; Wefel & Schagen, 2012; Jim et al., 2012). The underlying mechanisms of CRCI remain unclear, but there is consensus within the scientific community that the causes are multifactorial (Ahles et al., 2012; Argyriou et al., 2011; Jim et al., 2012). The findings from this study further support this notion. This study provides a unique contribution to the literature by illustrating the non-linear relationships between the selected psychosocial and behavioral variables and cytokines, and between the cytokines and the cognitive measures. The findings from this study also have clinical implications. Healthcare providers must acknowledge survivors'

concerns and assess cognitive functioning throughout the cancer trajectory. It is essential that providers recognize that these cognitive concerns may be influenced by many factors that extend far beyond the receipt of chemotherapy. This study provided new knowledge on inflammation and cognitive function six months to 10 years after breast cancer chemotherapy using a biobehavioral model to simultaneously evaluate modifiable psychosocial and behavioral factors that contribute to cognitive function in BCS. Findings from this study provide initial evidence for needed future prospective and translational studies to improve cognitive function in BCS.

Appendices

Appendix A IRB Approval Letter

OFFICE OF RESEARCH SUPPORT

THE UNIVERSITY OF TEXAS AT AUSTIN

P.O. Box 7426, Austin, Texas 78713 · Mail Code A3200
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FWA # 00002030

Date: 11/23/16

PI: Ashley M Henneghan

Dept: Nursing

Title: Biobehavioral Contributors to Cognition in Breast Cancer Survivors

Re: IRB Expedited Continuing Review Approval for Protocol Number 2015-10-0039

Dear Ashley M Henneghan:

In accordance with the Federal Regulations the Institutional Review Board (IRB) reviewed the above referenced research study continuing review report and found it met the requirements for approval under the Expedited category noted below for the following period of time: 12/11/2016 to 12/10/2017. *Expires 12 a.m. [midnight] of this date.*

Expedited category of approval:

☐ 1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met. (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review). (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

☐ 2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: (a) from healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or (b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

☒ 3) Prospective collection of biological specimens for research purposes by non-invasive means. Examples:

(a) Hair and nail clippings in a non-disfiguring manner.
(b) Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction.
(c) Permanent teeth if routine patient care indicates a need for extraction.
(d) Excreta and external secretions (including sweat).

(e) Uncannulated saliva collected either in an un-stimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue.
(f) Placenta removed at delivery.
(g) Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor.
(h) Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.
(i) Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings.
(j) Sputum collected after saline mist nebulization.

☐ 4) Collection of data through non-invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications).
Examples:
(a) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy.
(b) Weighing or testing sensory acuity.
(c) Magnetic resonance imaging.
(d) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography.
(e) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

☒ 5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).
Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.

☒ 6) Collection of data from voice, video, digital, or image recordings made for research purposes.

☐ 7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.
Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.

☒ Use the attached approved informed consent document(s).

☐ You have been granted a Waiver of Documentation of Consent according to 45 CFR 46.117 and/or 21 CFR 56.109(c)(1).

☐ You have been granted a Waiver of Informed Consent according to 45 CFR 46.116(d).

Appendix A IRB Approval Letter

Responsibilities of the Principal Investigator:

1. Report immediately to the IRB any unanticipated problems.

2. Submit for review and approval by the IRB all modifications to the protocol or consent form(s). Ensure the proposed changes in the approved research are not applied without prior IRB review and approval, except when necessary to eliminate apparent immediate hazards to the subject. Changes in approved research implemented without IRB review and approval initiated to eliminate apparent immediate hazards to the subject must be promptly reported to the IRB, and will be reviewed under the unanticipated problems policy to determine whether the change was consistent with ensuring the subjects continued welfare.

3. Report any significant findings that become known in the course of the research that might affect the willingness of subjects to continue to participate.

4. Ensure that only persons formally approved by the IRB enroll subjects.

5. Use only a currently approved consent form, if applicable.
   Note: Approval periods are for 12 months or less.

6. Protect the confidentiality of all persons and personally identifiable data, and train your staff and collaborators on policies and procedures for ensuring the privacy and confidentiality of subjects and their information.

7. Submit a Continuing Review Application for continuing review by the IRB. Federal regulations require IRB review of on-going projects no less than once a year a reminder letter will be sent to you two months before your expiration date. If a reminder is not received from Office of Research Support (ORS) about your upcoming continuing review, it is still the primary responsibility of the Principal Investigator not to conduct research activities on or after the expiration date. The Continuing Review Application must be submitted, reviewed and approved, before the expiration date.

8. Upon completion of the research study, a Closure Report must be submitted to the ORS.

9. Include the IRB study number on all future correspondence relating to this protocol.

If you have any questions contact the ORS by phone at (512) 471-8871 or via e-mail at orsc@uts.cc.utexas.edu.

Sincerely,

James P. Wilson

James Wilson, Ph.D.
Institutional Review Board Chair

Appendix B. Army of Women Approval

Appendix B Army of Women Approval Letter

Dr. Susan Love
RESEARCH FOUNDATION
For a future without breast cancer™

August, 29th 2016

Ashley Henneghan, MSN
University of Texas at Austin
1710 Red River St.
Austin, TX 78704

Dear Ashley Henneghan,

We are happy to write this letter to confirm that Dr. Susan Love Research Foundation's Army of Women (AOW) will serve as a recruitment source for your research study titled, Biobehavioral Contributors to Cognition in Breast Cancer Survivors. The AOW is a program of the Dr. Susan Love Research Foundation and was established through a grant from the Avon Foundation for Women, with the goal of accelerating research through a "just-in-time" tissue and data bank. To date, over 380,000 women and men–with and without a history of breast cancer and those at high risk–have signed up to be part of the AOW by indicating their willingness to consider participation in research. The diversity of the AOW members has proved beneficial for many studies, such as those needing to enroll breast cancer patients.

Scientists, such as yourself, contact the AOW because they need research participants, blood, urine, tissue, saliva and/or ductal fluid and/or information. Once a study has been funded, IRB-approved, and approved by the DSLRF Scientific Advisory Committee, an e-blast will be sent out to every AOW member, describing the study and criteria for entry. Our volunteers RSVP to the AOW website where a secondary screen takes place before the names and contact information are passed on to the researcher.

If there are further questions, please do not hesitate to contact Amaka Obidegwu, Project Research Manager, at aobidegwu@drsusanloveresearch.org or 310-828-0060 x130.

Sincerely,

Susan Love, MD, MBA
Chief Visionary Officer
Dr. Susan Love Research Foundation

16133 Ventura Blvd, Suite 1000 Encino, CA 91436 tel 310-828-0060 fax 310-828-5403
www.DrSusanLoveResearch.org

Appendix C. Army of Women E Blast Letter

Subject Line: **Memory and Learning Problems After Breast Cancer**

Banner: Women who received chemotherapy for breast cancer needed for study on brain functioning

We need women living in or willing to travel to Austin, TX, who were diagnosed with stage I, II, or III breast cancer to participate in a study about factors that may contribute to thinking, understanding, learning, and memory problems following chemotherapy.

Women who receive chemotherapy as part of their breast cancer treatment are at increased risk of developing problems with thinking and brain functioning—often called "chemobrain." These memory and learning problems can reduce quality of life. Why some women develop these problems and others do not isn't clear. This study is looking at whether inflammation—the body's protective response— and inflammatory pathways might be factors. Other studies have found that stress, physical activity, social isolation, and sleep are associated with both inflammation and cognitive function in certain groups of people. The research team hopes to determine if this is also true in women with breast cancer who have been treated with chemotherapy.

Please read on to learn more about what is involved and who can participate. If this study isn't right for you, please pass it on to your family members or friends.

What's the study about?

The purpose of this study is to identify psychosocial factors (stress, social isolation) and behavioral (physical activity, sleep quality) factors that may be associated with inflammation as well as contribute to thinking (memory, attention, and processing speed) problems following chemotherapy.

What's involved?

If you agree to participate in the Biobehavioral Contributors to Cognition in Breast Cancer Survivors study, you will be asked to go to the School of Nursing at the University of Texas at Austin to do the following:

- Complete a written survey.
- Undergo cognitive (thinking) tests to assess memory, attention, processing speed, and executive function.
- Have your height and weight and your hip and waist circumference measured.
- Have your blood drawn (1-2 tubes, up to 20 ml).
- These activities will take approximately 60 minutes to complete.

Appendix C. Army of Women E Blast Letter

Appendix C Army of Women E Blast Letter

This study will take 1 hour of your time not including time driving to and from the School of Nursing at the University of Texas at Austin.

Who is conducting the study?

Ashley Henneghan, RN, BSN, MSN, University of Texas at Austin Doctoral Candidate

Where?

University of Texas at Austin

Who can participate?

You can join the Biobehavioral Contributors to Cognition in Breast Cancer Survivors study if you match ALL of these MAIN categories:

- You are a female between the ages of 21 and 65
- You have been diagnosed with breast cancer (Stages I-III)
- You received chemotherapy as part of your treatment, and have been without evidence of disease for 6 months to 10 years. It is okay if you are taking hormone therapy (e.g. tamoxifen)
- You are able to read and write English
- You are willing and able to travel to University of Texas at Austin for the study visit.

After you RSVP and if you are eligible, the research team will follow up with you for the next steps in the study.

Appendix D. Recruitment Site Letter of Support- Texas Oncology

TEXAS ONCOLOGY

February 20, 2015

Ashley M. Henneghan, MSN, BSN, RN
Doctoral Student
1710 Red River St.
Austin TX, 78701

RE: Biobehavioral *Contributors* to Cognition in Breast Cancer Survivors

Dear Ms. Henneghan,

It is my pleasure as Director of Supportive Care Programs at Texas Oncology to provide this letter of support for your NRSA proposal entitled *"Biobehavioral Contributors to Cognition in Breast Cancer Survivors".*

Texas Oncology has 5 locations in the Austin area providing comprehensive cancer care to a diverse group of cancer patients and survivors. As you know, we offer survivorship services and follow our survivors for several years after primary treatment has ended. **More than 3,300** of our patients in the Austin Area have a history of breast cancer.

Research on cancer related cognitive dysfunction is highlighted as a research priority of both the National Cancer Institute Office of Survivorship and President's Cancer Panel. Identifying modifiable factors that may be contributing to cognitive function is essential for moving the science forward. Clinicians understand the importance of this research area and Texas Oncology, a statewide oncology provider serving thousands of patients, will support your doctoral research as a recruitment site in the future. More specifically, we will put recruiting fliers up at our Central Texas- Austin locations along with educating our providers and clinical staff about the study's inclusion criteria.

While working with our organization over the past two years you have demonstrated your clinical experience, intellect, motivation and affinity for research, especially while collaborating with Dr. Becker on the recent study aimed to improve cognitive function for breast cancer survivors up to 5 years after treatment. You show great promise for becoming a distinguished nurse leader and an expert oncology researcher.

6204 Balcones Drive ♦ Austin, Texas 78731
Phone: (512) 427-9400 ♦ Fax: (512) 342-2723

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Appendix D. Recruitment Site Letter of Support- Texas Oncology

TEXAS ONCOLOGY

Texas Oncology will gladly assist with your recruitment efforts for this important research project. We anticipate similar recruitment rates as Dr. Becker's current research project that targets the same population. I am pleased to give you my strongest recommendation and encourage a favorable decision for this proposal.

Sincerely,

Sabrina Q. Mikan, PhD, RN, ACNS-BC
Director, Supportive Care Programs
6204 Balcones Drive
Austin, TX 78731
(512) 427-9461
sabrina.mikan@usoncology.com

6204 Balcones Drive ♦ Austin, Texas 78731
Phone: (512) 427-9400 ♦ Fax: (512) 342-2723

Appendix E. Recruitment Site Letter of Support- Breast Cancer Resource Center

BREAST CANCER RESOURCE CENTERS OF TEXAS

March 6, 2015

Ashley M. Henneghan, MSN, BSN, RN
Doctoral Student
1710 Red River St.
Austin TX, 78701

Dear Ms. Henneghan,

As Executive Director of the Breast Cancer Resource Center (BCRC), I fully endorse your proposed study concerning the identification modifiable factors that contribute to cognitive function after breast cancer.

The BCRC serves all those touched by breast cancer in Central Texas including a diverse group of breast cancer survivors. We know that cognitive concerns are very common during and after treatment. These concerns can be devastating to survivors—interrupting employment, disrupting relationships, and ultimately contributing to a poor quality of life. Unfortunately, there is limited information on this troubling treatment side effect and no treatment options. We have appreciated your voluntary services to the BCRC over the last year providing educational programs to our survivor support groups in addition to your expert blog posting (shared by more than 400 of our members through social media).

Understanding what contributes to cognitive dysfunction after breast cancer treatment is critical to developing treatment options for patients and survivors. Our center is committed to assisting in recruitment for your study by allowing you to educate our navigators on the study and inclusion criteria; providing information to survivors through our support groups (in person and online support groups), and posting study information online through our social media websites. As you know these recruitment strategies have proven successful for Dr. Becker's current study aimed to improve cognitive function of breast cancer survivors. We gladly support your research study, "Biobehavioral *Contributors* to Cognition in Breast Cancer Survivors".

Sincerely,

Ray Anne Evans
Executive Director
3006 Medical Arts Street
Austin, TX 78705

Appendix F. Recruitment Site Letter of Support- Central Texas Oncology Nursing Society

February 19, 2015

Ashley M. Henneghan, MSN, BSN, RN
Doctoral Student
1710 Red River St.
Austin TX, 78701

Dear Ms. Henneghan,

As the former President of the Central Texas Oncology Nursing Society (CTONS), I fully support your proposed study, "Biobehavioral *Contributors* to Cognition in Breast Cancer Survivors". Clinical guidelines to manage cognitive problems after treatment are lacking; therefore, oncology nurses are limited in their abilities to educate and offer symptom management to these patients. Your proposed research is critical to advancing nursing science so that we can provide optimal survivorship care.

CTONS has over 200 members in the greater Austin area, with nurses from various oncology settings including the major Austin hospital systems (Seton and St. David's), community oncology centers (Texas Oncology, Austin Cancer Centers), home health care agencies (Health Sense Home Health, Hospice Austin), and oncology nursing education organizations (NOEP). Many of our nurses are employed as nurse navigators for breast cancer and are in ideal positions to identify potential participants and provide study information to breast cancer survivors. Our organization is committed to assisting with your recruitment by allowing you to present your study and inclusion criteria to our members at monthly meetings and providing recruitment information to all of our members through email communication including our quarterly newsletter.

Your proposed research concerning modifiable factors that contribute to cognitive function after breast cancer is very important. CTONS enthusiastically supports your proposal.

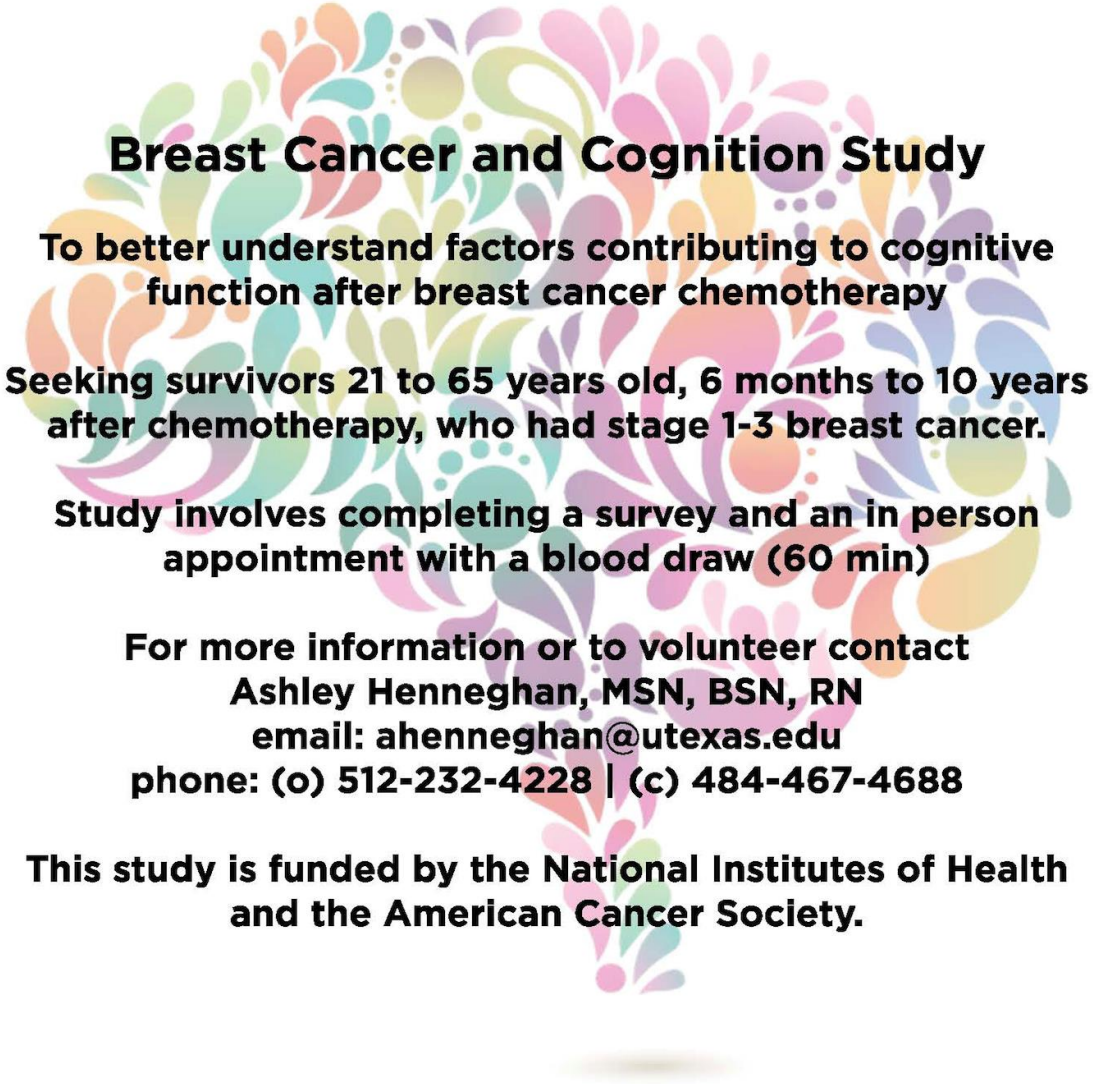
Sincerely,

Hannah Lopez

Hannah Lopez, MSN, RN
Former-President, current Executive Board Member
Central Texas Oncology Nursing Society

Appendix G. Recruitment Flyer

Appendix G Study Recruitment Flyer



Appendix H. Pre-screening Form

Phone Pre-Screening Form

"Biobehavioral Contributors to Cognition in Breast Cancer Survivors"

Thank you for calling about our new study -" **Biobehavioral Contributors to Cognition in Breast Cancer Survivors**". I would like to tell you a little about the study and then ask you a few questions to see if you would qualify to participate in the study.

This study is examining factors that may be contributing to cognitive function after breast caner treatment ends. You would be asked to sign an informed consent, complete a questionnaire, complete cognitive testing, have height, weight, waist circumference measured, and have two tubes of blood drawn.

Date and time of verbal request to participate in the study _____

Name _____

Phone Numbers: (Where is it best to contact you? Circle where best to contact by phone: Also, is it okay to leave messages for you at that number?)

Home: _____

Work: _____

Other: _____FAX #: _____

Mailing Address: _____

_____

Email contact: If yes, what is your email address? _____

Date:_____ Pre-Screen Interviewer initials: _____

So just a few questions - *<If the participant does not meet any of the qualifications, they will be thanked and told they are not eligible to be in the study>*

- What is your current age? _____DOB:_____(must be between 21-65 yrs.).
- What type of breast cancer were you diagnosed with?_____ (if inflammatory, thank applicant and close interview)
- What stage of breast cancer were you diagnosed with?_____ (if stage 4 (metastatic), thank applicant and close interview)
- Did you receive chemotherapy as part of your breast cancer treatment? Yes_____No_____*(if no, thank applicant and close interview).*
- What is the date of your last chemotherapy treatment?_____ *(if **less than 6 months or greater than 10**, get date and see if want to participate in the future) thank applicant and close interview)*
- Do you live close enough to (the University of Texas at Austin) that you would be able to come for testing? Yes___, No___ *(if no, thank applicant and close interview).*
- Is English your primary language for speaking and reading? Yes___, No___ *(if no, thank applicant and close interview).*

Appendix H. Pre-screening Form

Appendix H Phone Prescreening Form

- Has a doctor ever diagnosed you with or told you, you had: a stroke__encephalitis__traumatic brain injury__brain surgery__ dementia__Alzheimer's disease, or Parkinson's disease__history of cranial radiation therapy or chemotherapy in your spinal cord __current unmanaged major depression__ substance abuse__ or history of unmanaged bipolar disorder__, psychosis__schizophrenia__ or verbal learning disability (diagnosed by a psychologist or a physician)__ current cancer__RA__Narcolepsy__ Restless Leg Syndrome__Unmanaged Sleep Apnea__Type 2 DM?__

If yes, thank applicant and close interview.

- Do you have any other medical conditions that might keep you from participating in this project? Yes, please describe:

  _____
  _____,
  No _____.
  Have you taken oral steroids in the last 3 months? Yes, ____ *(if **yes**, get date and see if want to participate in the future) thank applicant and close interview)*,
  No _____.

  Are you currently taking any *biologic response modifiers* medications (such as Humira)? Yes, ____ *(if **yes**, get date and see if want to participate in the future) thank applicant and close interview)*,
  No _____.
  Race and Ethnic questions (They may choose not to answer.)

- Are you Spanish/Hispanic/Latino?
  0 = No, not Spanish/Hispanic/Latino
  1 = Yes, I am Spanish/Hispanic/Latino
  Missing = no response given

- Which of the following best describes your race?
  (They can give more than one answer.)
  1 = American Indian or Alaska Native
  2 = Asian
  3 = Native Hawaiian and Other Pacific Islander
  4 = Black or African American
  5 = White
  6 = Other (Please describe) _____
  7 = Multiple categories chosen

- What are the most convenient times for you to be tested? *(schedule 90 minute appointment)*

Date of testing:_____

Other Notes or Comments:
_____

Appendix I. Consent Form

IRB USE ONLY
Study Number: 2015-10-0039
Approval Date: 12/11/2016
Expires: 12/10/2016
Name of Funding Agency: American Cancer Society

Consent for Participation in Research
Title: Biobehavioral Contributors to Cognition in Breast Cancer Survivors

Introduction

The purpose of this form is to provide you information that may affect your decision as to whether or not to participate in this research study. The person performing the research will answer any of your questions. Read the information below and ask any questions you might have before deciding whether or not to take part. If you decide to be involved in this study, this form will be used to record your consent.

Purpose of the Study

You have been asked to participate in a research study about **understanding factors that influence inflammation and cognitive function in breast cancer survivors**. The purpose of this study **is to identify modifiable psychosocial and behavioral factors that may contribute to cognitive function both directly and indirectly through biological factors (inflammatory markers) in 180 breast cancer survivors (ages 21 to 65) 6 months to ten years after chemotherapy.**

What will you be asked to do?

If you agree to participate and travel to the School of Nursing for this study, you will be asked to:

- Complete a survey
- Undergo Cognitive Testing for approximately 60 min
- Have your height, weight, and hip and waist circumference measured
- Have your blood drawn (1-2 tubes, up to 20 ml) using aseptic technique

If you agree to participate in this study and are unable to travel to the school, you will be asked to

- Complete a survey
- Undergo Cognitive Testing for approximately 30 min
- No blood samples will be taken

This study will take **up to 3 hours of your time for travel to the School of Nursing, completion of survey, testing, height and weight, and blood draw.** This study will include approximately **180** study participants. Note that your blood sample will be kept for up to 5 years to be used by this investigator in future analyses, but no identifiable information will be attached to the blood sample.

NOTE: Aseptic technique includes sterile and/or disposable equipment (e.g., blood collection apparatus) and adherence to standard medical precautions.

What are the risks involved in this study?

This study may involve some risks. Persons who participate in the study may already have concerns about their cognitive function that might be a source of distress. You may become upset or frustrated, or experience increased feelings (depression, anxiety, and anger) when completing the various cognitive tests. Completing the study may be an inconvenience to you. This study contains one invasive procedure, venipuncture (inserting a needle into a vein in the arm and withdrawing a sample of blood). Venipuncture during data collection poses a

Appendix I. Consent Form

risk of localized discomfort (likely but brief), bleeding, hematoma, and infection (all unlikely). In some cases, it may be difficult to obtain a serum sample due to small or fragile veins. The other procedures in this study are noninvasive, and the data obtained should not expose you to any psychological, social, or legal risks. We do not expect that these risks will be greater than those experienced in meeting the cognitive, physical, and emotional demands of you everyday life as a cancer survivor.

What are the possible benefits of this study?

You will receive no direct benefit from participating in this study; however, a possible benefit of participation is **knowing you are helping with the development of new knowledge that may help other cancer survivors.**

Do you have to participate?

No, your participation is voluntary. You may decide not to participate at all or, if you start the study, you may withdraw at any time. Withdrawal or refusing to participate will not affect your relationship with The University of Texas at Austin or your health care providers in any way.

If you would like to participate **sign this form and return to the researcher in person**. You will receive a copy of this form.

Will there be any compensation?

You will receive **a $10 gift card to Amazon or Starbucks (your choice) immediately following your appointment.**

What if you are injured because of the study?

The University has no program or plan to provide treatment for research-related injury or payment in the event of a medical problem. In the event of a research related injury, please contact the principal investigator.

The University has no program or plan for continuing medical care and/or hospitalization for research-related injuries or for financial compensation."

How will your privacy and confidentiality be protected if you participate in this research study?

Your privacy and the confidentiality of your data will be protected by keeping signed consent forms separate from data files in locked cabinets. You will be assigned a unique ID number that will be written on your surveys and blood work to maintain confidentiality of data. A separate list of names with assigned data record identification numbers will be kept on the applicant's computer in a password-protected file.

If it becomes necessary for the Institutional Review Board to review the study records, information that can be linked to you will be protected to the extent permitted by law. Your research records will not be released without your consent unless required by law or a court order. The data resulting from your participation may be made available to other researchers in the future for research purposes not detailed within this consent form. In these cases, the data will contain no identifying information that could associate it with you, or with your participation in any study.

Whom to contact with questions about the study?

Appendix I. Consent Form

Prior, during or after your participation you can contact the researcher **Ashley Henneghan, RN, BSN, MSN** at **512-475-8794** or send an email to **ahenneghan@utexas.edu** for any questions or if you feel that you have been harmed. **Or you can contact Alexa Stuifbergen, RN, Ph.D, FAAN at 512-471-4100 or send an email to astuifbergen@mail.nur.utexas.edu.**

This study has been reviewed and approved by The University Institutional Review Board and the study number is **[STUDY NUMBER].**

Whom to contact with questions concerning your rights as a research participant?

For questions about your rights or any dissatisfaction with any part of this study, you can contact, anonymously if you wish, the Institutional Review Board by phone at (512) 471-8871 or email at orsc@uts.cc.utexas.edu.

Participation

If you agree to participate **sign and return to the researcher in person at your appointment.**

Signature

You have been informed about this study's purpose, procedures, possible benefits and risks, and you have received a copy of this form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask other questions at any time. You voluntarily agree to participate in this study. By signing this form, you are not waiving any of your legal rights.

_____
Printed Name

_____ _____
Signature Date

As a representative of this study, I have explained the purpose, procedures, benefits, and the risks involved in this research study.

_____
Print Name of Person obtaining consent

_____ _____
Signature of Person obtaining consent Date

Appendix J. Study Instruments

Background and Treatment Information

1. What is your date of birth? ___/___/_____
   MM/DD/YEAR

Please answer BOTH questions 2 and 3:

2. Are you Spanish/Hispanic/Latino?
   ____No, not Spanish/Hispanic/Latino
   ____Yes, I am Spanish/Hispanic/Latino

3. Which of the following best describes your race?
   (You can circle more than one answer.)

   1 American Indian or Alaska Native
   2 Asian
   3 Native Hawaiian and Other Pacific Islander
   4 Black or African American
   5 White
   6 Other (Please describe) _____

4. What is your present marital status?
   1 Never Married
   2 Married
   3 Divorced
   4 Widowed
   5 Separated
   6 Living with a significant other

5. Do you have children?
   0 No
   1 Yes

6. How many years of school have you completed? (For example, if you completed high school (12years) and received a bachelor's degree (4 years) you would put 16) _____

7. What is the highest diploma/degree that you have completed in school?
   1 No diploma/degree
   2 Vocational Training or Certificate
   3 GED
   4 High School Diploma
   5 Associate Degree
   6 Bachelors Degree
   7 Graduate Degree (Masters or Doctoral)

8. What is your **CURRENT** employment status? (Please circle only one choice.)
   1 I work full-time for pay (Includes farm/ranch work)
   2 I work part-time for pay (Includes farm/ranch work)
   3 I am a full-time homemaker
   4 I am a full-time homemaker and also help with farm/ranch work
   5 I am a full-time homemaker and also work part-time at another job
   6 I am unemployed due to age
   7 I am unemployed due to disability
   8 I am laid off
   9 I have been fired
   10 I am a full-time student
   11 I am a student (full- or part-time) and also work for pay
   12 I have been unable to find suitable work because of where I live
   13 I am retired

9. If you are employed, how many hours a week do you work? _____
   Please describe what kind of business or industry you work in:

Appendix J. Study Instruments

10. What was your employment status **PRIOR** to your breast cancer diagnosis? (Please circle only one choice.)
    1 I worked full-time for pay (Includes farm/ranch work)
    2 I worked part-time for pay (Includes farm/ranch work)
    3 I was a full-time homemaker
    4 I was a full-time homemaker and also help with farm/ranch work
    5 I was a full-time homemaker and also work part-time at another job
    6 I was unemployed due to age
    7 I was unemployed due to disability
    8 I was laid off
    9 I had been fired
    10 I was a full-time student
    11 I was a student (full- or part-time) and also worked for pay
    12 I was been unable to find suitable work because of where I liveed
    13 I was retired

11. If you **were** employed, how many hours a week **did** you work prior to your breast cancer diagnosis? _____
    Please describe what kind of business or industry you worked in prior to your diagnosis:

12. If there have been any changes in your work situation since your cancer experience, please describe the changes:

13. What is your annual household income?
    1 $0-50,000
    2 $50,000-99,999
    3 $100,000- 149,000
    4 $150,000-199,999
    5 $200,00 or more

14. What was your annual household income PRIOR TO your breast cancer diagnosis?
    1 $0-50,000
    2 $50,000-99,999
    3 $100,000- 149,000
    4 $150,000-199,999
    5 $200,00 or more

15. When were you diagnosed with breast cancer (MM/YY)?_____

16. What type of breast cancer were you diagnosed with?
    1 Ductal carcinoma in situ (DCIS; also known as *intraductal carcinoma*)
    2 Invasive (or infiltrating) ductal carcinoma (IDC)
    3 Invasive (or infiltrating) lobular carcinoma (ILC)
    4 Other_____

17. Did you receive genetic testing for your breast cancer?
    1 Yes
    2 No

18. If answer to question 17 is "yes", what type of results did you get? Circle all that apply
    1 BRCA 1 positive
    2 BRCA 1 negative
    3 BRCA 2 positive
    4 BRCA 2 negative

19. Was your breast cancer diagnosed with receptor status?

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1 Yes
2 No

20. If answer to question 19 is yes, what type of receptor status?
1 Estrogen-receptor positive (ER+)
2 Estrogen-receptor negative (ER-)
3 Progesterone-receptor positive (PR+)
4 Progesterone-receptor positive (PR-)
5 HER+
6 HER-
7 Triple Negative
8 Other_____

21. What types of treatments did you receive for your breast cancer treatment? **Circle all that apply and check specific type (s) of treatment underneath each treatment type**
1 Surgery
__ Lumpectomy
__ Mastectomy
__ Double mastectomy
Other _____
2 Radiation
How many days a week? _____
How many weeks? _____
3 Chemotherapy
___ doxorubicin (Adriamycin, Doxil)
___ methotrexate (Amethopterin, Mexate, Folex)
___ paclitaxel (Taxol)
___ docetaxel (Taxotere)
___ fluorouracil, 5- fluorouracil, 5-FU (Adrucil)
___ carboplatin (Paraplatin)
___ cyclophosphamide (Cytoxan)
___ Other (please specify)_____
4 Hormonal Therapy
___ Aromatase Inhibitors (e.g. Arimidex®, Aromasin®, Femara®)
___ Selective Estrogen Receptor Modulators (e.g. tamoxifen, Evista®, Fareston®)
___ Estrogen Receptor down regulators (e.g. Faslodex®)
5 Herceptin
6 Other _____

22. What was the date of your last chemotherapy treatment (MM/YY)?_____

Appendix J. Study Instruments

23. What is your menopausal status?

__ premenopausal _____ peri-menopausal ____have gone through menopause

___ chemical or surgical induced menopause

24. When was your last menstrual period?_____

What treatments are you presently using for your breast cancer Treatment? (✓ all that apply)

_____	$_0$ No medications	_____	$_3$ Selective Estrogen Receptor Modulators (e.g. tamoxifen, Evista®, Fareston®)
_____	$_1$ Steroids		
_____	$_2$ Aromatase Inhibitors (e.g. Arimidex®, Aromasin®, Femara®)	_____	$_4$ Estrogen Receptor down regulators (e.g. Faslodex®)

All other prescription medications (Please list or add an additional sheet with your list) _____

_____

_____

_____

Appendix J. Study Instruments

Charlson Co-morbidity Index

Charlson, et al. Co-Morbidity Index	
Please check if you have any of the following conditions:	
_____ 1	Hypertension
_____ 2	Ulcer disease
_____ 3	Arthritis
_____ 4	Mild liver disease
_____ 5	Severe liver disease
_____ 6	Heart attack/Myocardial infarction/MI
_____ 7	Cancer (solid tumor)
_____ 8	Cancer (metastatic)
_____ 9	Lymphoma
_____10	AIDS/HIV
_____11	Diabetes with no damage to eyes, feet or kidneys
_____12	Diabetes with damage to eyes, feet or kidneys
_____13	Stroke/CVA with no paralysis
_____14	Stroke/CVA that left you partially paralyzed
_____15	Moderate or severe kidney damage
_____16	Chronic pulmonary disease/COPD/Emphysema
_____17	Congestive Heart Failure
_____18	Dementia
_____19	Peripheral vascular disease (Claudication)
_____20	Leukemia

Other medical conditions not mentioned above: _____
Other mental health conditions: _____

_____

(Charlson, et al. 2000; Luber, et al. 2000)

Appendix J. Study Instruments

International Physical Activity Questionnaire

Instructions: We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions are about the time you spent being physically active in the last 7 days. They include questions about activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Your answers are important.

Please answer each question even if you do not consider yourself to be an active person.

In answering the following questions,
- **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder that normal.
- **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder that normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY
The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?
   □ Yes
   □ No ➔ *Skip to PART 2: TRANSPORTATION*

The next questions are about all the physical activity you did in **the last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, heavy construction, or climbing up stairs as part of your work? Think about only those physical activities that you did for at least 10 minutes at a time.
   _____ days per week
   □No vigorous job-related physical activity ➔ *Skip to question 4*

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?
   _____ hours per day
   _____ minutes per day

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads as **part of your work**? Please do not include walking.
   _____ days per week
   □No moderate job-related physical activity ➔ *Skip to question 6*

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?
   _____ hours per day
   _____ minutes per day

6. During **the last 7 days**, on how many days did you **walk** for at least 10 minutes at a time

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as part of your work? Please do not count any walking you did to travel to or from work.
_____ days per week
□No job-related walking ➔ *Skip to PART 2: TRANSPORTATION*

7. How much time did you usually spend on one of those days **walking** as part of your work?
_____ hours per day
_____ minutes per day

PART 2: TRANSPORTATION PHYSICAL ACTIVITY
These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the **last 7 days**, on how many days did you travel **in a motor vehicle** like a train, bus, car, or tram?
_____ days per week
□No traveling in a motor vehicle ➔ *Skip to question 10*

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?
_____ hours per day
_____ minutes per day

Now think only about the bicycling and walking you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go **from place to place**?
_____ days per week
□No bicycling from place to place ➔ *Skip to question 12*

11. How much time did you usually spend on one of those days to **bicycle** from place to place?
_____ hours per day
_____ minutes per day

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?
_____ days per week
□No walking from place to place ➔ *Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY*

13. How much time did you usually spend on one of those days **walking** from place to place?
_____ hours per day
_____ minutes per day

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PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the **last 7 days** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days,** on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging in the garden or yard?
_____ days per week
□No vigorous activity in garden or yard ➔ *Skip to question 16*

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?
_____ hours per day
_____ minutes per day

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking in the garden or yard?
_____ days per week
□No moderate activity in garden or yard ➔ *Skip to question 18*

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?
_____ hours per day
_____ minutes per day

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During **the last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?
_____ days per week
□No moderate activity inside home ➔ *Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY*

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?
_____ hours per day
_____ minutes per day

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the last 7 days solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?
_____ days per week
□No walking in leisure time ➔ *Skip to question 22*

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21. How much time did you usually spend on one of those days **walking** in your leisure time?
_____ hours per day
_____ minutes per day

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming in your leisure time?
_____ days per week
□No vigorous activity in leisure time ➔ *Skip to question 24*

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?
_____ hours per day
_____ minutes per day

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis in your leisure time?
_____ days per week
□No moderate activity in leisure time ➔ *Skip to PART 5: TIME SPENT SITTING*

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?
_____ hours per day
_____ minutes per day

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?
_____ hours per day
_____ minutes per day

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend** day?
_____ hours per day
_____ minutes per day

Appendix J. Study Instruments

The Perceived Stress Scale

Perceived Stress Scale

The questions in this scale ask you about your feelings and thoughts during the last 7 days. In each case, you are asked to indicate by circling how often you felt or thought a certain way.

0 = Never
1 = Almost Never
2 = Sometimes
3 = Fairly Often
4 = Very Often

1. In the last month, how often have you been upset because of something that happened unexpectedly?	0	1	2	3	4
2. In the last month, how often have you felt that you were unable to control the important things in your life?	0	1	2	3	4
3. In the last month, how often have you felt nervous and "stressed"?	0	1	2	3	4
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	0	1	2	3	4
5. In the last month, how often have you felt that things were going your way?	0	1	2	3	4
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	0	1	2	3	4
7. In the last month, how often have you been able to control irritations in your life?	0	1	2	3	4
8. In the last month, how often have you felt that you were on top of things?	0	1	2	3	4
9. In the last month, how often have you been angered because of things that were outside of your control?	0	1	2	3	4
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

If you experience stress regularly, what are the causes of your stress?

Appendix J. Study Instruments

UCLA Loneliness Scale

Indicate how often each of the statements below is descriptive of how you felt in the last 7 days. Click on one letter for each statement:

A indicates "I always feel this way"
S indicates "I sometimes feel this way"
R indicates "I rarely feel this way"
N indicates "I never feel this way"

1*	How often do you feel that you are "in tune" with the people around you?	A	S	R	N
2	How often do you feel that you lack companionship?	A	S	R	N
3	How often do you feel that there is no one you can turn to?	A	S	R	N
4	How often do you feel completely alone?	A	S	R	N
5*	How often do you feel part of a group of friends?	A	S	R	N
6*	How often do you feel that you have a lot in common with the people around you?	A	S	R	N
7	How often do you feel that you are no longer close to anyone?	A	S	R	N
8	How often do you feel that your interests and ideas are not shared by those around you?	A	S	R	N
9*	How often do you feel outgoing and friendly?	A	S	R	N
10*	How often do you feel close to people?	A	S	R	N
11	How often do you feel left out?	A	S	R	N
12	How often do you feel that your relationships with others are not meaningful?	A	S	R	N
13	How often do you feel that no one really knows you well?	A	S	R	N
14	How often do you feel isolated by others?	A	S	R	N
15*	How often do you feel you can find companionship when you want it?	A	S	R	N
16*	How often do you feel that there are people who really understand you?	A	S	R	N
17	How often do you feel shy?	A	S	R	N
18	How often do you feel that people are around you but not with you?	A	S	R	N
19*	How often do you feel that there are people you can talk to?	A	S	R	N
20*	How often do you feel that there are people you can turn to?	A	S	R	N

Russell, D. (1996). The UCLA Loneliness Scale (Version 3): Reliability, validity, and factor structure. Journal of Personality Assessment, 66, 20-40.

Appendix J. Study Instruments

PITTSBURGH SLEEP QUALITY INDEX

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past 7 days only. Your answers should indicate the most accurate reply for the majority of days and nights in the past 7 days only. Please answer all questions.

1. During the past 7 days, what time have you usually gone to bed at night?

BED TIME _____

2. During the past 7 days, how long (in minutes) has it usually taken you to fall asleep each night?

NUMBER OF MINUTES _____

3. During the past 7 days, what time have you usually gotten up in the morning?

GETTING UP TIME _____

4. During the past 7 days, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past 7 days, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes

Not during the past 7 days _____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

b) Wake up in the middle of the night or early morning

Not during the past 7 days _____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

c) Have to get up to use the bathroom

Not during the past 7 days _____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

d) Cannot breathe comfortably

Not during the past 7 days _____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Cough or snore loudly

Not during the past 7 days _____ Less than once a week_____ Once or twice a week_____ Three or more

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times a week_____
f) Feel too cold

Not during the past 7 days _____ Less than once a week_____ Once or twice a week_____ Three or more

times a week_____

g) Feel too hot

Not during the past 7 days _____ Less than once a week_____ Once or twice a week_____ Three or more

times a week_____

h) Had bad dreams

Not during the past 7 days _____ Less than once a week_____ Once or twice a week_____ Three or more

times a week_____

i) Have pain

Not during the past 7 days _____ Less than once a week_____ Once or twice a week_____ Three or more

times a week_____

j) Other reason(s), please describe_____
_____

How often during the past month have you had trouble sleeping because of this?

Not during the past 7 days _____ Less than once a week_____ Once or twice a week_____ Three or more

times a week_____

6. During the past 7 days, how would you rate your sleep quality overall?

Very good _____
Fairly good _____
Fairly bad _____
Very bad _____

7. During the past 7 days, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past 7 days _____ Less than once a week_____ Once or twice a week_____ Three or more

times a week_____

8. During the past 7 days, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past 7 days _____ Less than once a week_____ Once or twice a week_____ Three or more

times a week_____

Appendix J. Study Instruments

9. During the past 7 days, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____
Only a very slight problem _____
Somewhat of a problem _____
A very big problem _____

10. Do you have a bed partner or room mate?

No bed partner or room mate _____

Partner/room mate in other room _____

Partner in same room, but not same bed _____

Partner in same bed _____

If you have a room mate or bed partner, ask him/her how often in the past ~~month~~ 7 days you have had . . .

a) Loud snoring
Not during the past 7 days _____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

b) Long pauses between breaths while asleep

Not during the past 7 days _____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____
c) Legs twitching or jerking while you sleep

Not during the past 7 days _____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

d) Episodes of disorientation or confusion during sleep

Not during the past 7 days _____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Other restlessness while you sleep; please describe_____
Not during the past 7 days _____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

Appendix J. Study Instruments

Epworth Sleepiness Scale
How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?
This refers to your usual way of life in recent times
Even if you haven't done some of the things recently, try to work out how they would have affected you.

Use the Following scale to choose **the most appropriate** number for each situation.

0= would NEVER doze
1= SLIGHT chance of dozing
2= MODERATE CHANCE of dozing
3= HIGH CHANCE of dozing

It is important that you answer each question as best you can

Situation	Chance of Dozing (0-3)
Sitting and Reading	___
Watching TV	___
Sitting, inactive in a public place (e.g. theatre or meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after lunch without alcohol	___
In a car while stopped for a few minutes in traffic	___

Appendix J. Study Instruments

FACT-Cognitive Function (Version 3)

Below is a list of statements that other people with your condition have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Never	About once a week	Two to three times a week	Nearly every day	Several times a day
	I have had trouble forming thoughts.....	0	1	2	3	4
	My thinking has been slow.....	0	1	2	3	4
	I have had trouble concentrating	0	1	2	3	4
	I have had trouble finding my way to a familiar place.....	0	1	2	3	4
	I have had trouble remembering where I put things, like my keys or my wallet	0	1	2	3	4
	I have had trouble remembering new information, like phone numbers or simple instructions	0	1	2	3	4
	I have had trouble recalling the name of an object while talking to someone	0	1	2	3	4
	I have had trouble finding the right word(s) to express myself	0	1	2	3	4
	I have used the wrong word when I referred to an object	0	1	2	3	4
	I have had trouble saying what I mean in conversations with others	0	1	2	3	4
	I have walked into a room and forgotten what I meant to get or do there	0	1	2	3	4
	I have had to work really hard to pay attention or I would make a mistake	0	1	2	3	4
	I have forgotten names of people soon after being introduced	0	1	2	3	4
	My reactions in everyday situations have been slow.....	0	1	2	3	4
	I have had to work harder than usual to keep track of what I was doing	0	1	2	3	4
	My thinking has been slower than usual	0	1	2	3	4
	I have had to work harder than usual to express myself clearly	0	1	2	3	4
	I have had to use written lists more often than usual so I would not forget things	0	1	2	3	4
	I have trouble keeping track of what I am doing if I am interrupted.....	0	1	2	3	4
	I have trouble shifting back and forth between different activities that require thinking	0	1	2	3	4
	Other people have told me I seemed to have trouble remembering information	0	1	2	3	4
	Other people have told me I seemed to have trouble speaking clearly.....	0	1	2	3	4
	Other people have told me I seemed to have trouble thinking clearly	0	1	2	3	4
	Other people have told me I seemed confused	0	1	2	3	4
		Never	About	Two to	Nearly	Several

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			once a week	three times a week	every day	times a day
	I have been able to concentrate	0	1	2	3	4
	I have been able to bring to mind words that I wanted to use while talking to someone	0	1	2	3	4
	I have been able to remember things, like where I left my keys or wallet	0	1	2	3	4
	I have been able to remember to do things, like take medicine or buy something I needed.....	0	1	2	3	4
	I am able to pay attention and keep track of what I am doing without extra effort.....	0	1	2	3	4
	My mind is as sharp as it has always been.....	0	1	2	3	4
	My memory is as good as it has always been	0	1	2	3	4
	I am able to shift back and forth between two activities that require thinking	0	1	2	3	4
	I am able to keep track of what I am doing, even if I am interrupted	0	1	2	3	4
	I have been upset about these problems.....	0	1	2	3	4
	These problems have interfered with my ability to work	0	1	2	3	4
	These problems have interfered with my ability to do things I enjoy.....	0	1	2	3	4
	These problems have interfered with the quality of my life	0	1	2	3	4

Last Revised 10 February 2008

Appendix J. Study Instruments

Please respond to each item by marking one box per row.

In the past 7 days:	Never	Rarely (Once)	Some-times (2 or 3 times)	Often (about once a day)	Always (Several times a day)
1. I felt fearful	☐1	☐2	☐3	☐4	☐5
2. I found it hard to focus on anything other than my anxiety	☐1	☐2	☐3	☐4	☐5
3. My worries overwhelmed me	☐1	☐2	☐3	☐4	☐5
4. I felt uneasy	☐1	☐2	☐3	☐4	☐5
5. I felt nervous	☐1	☐2	☐3	☐4	☐5
6. I felt like I needed help for my anxiety	☐1	☐2	☐3	☐4	☐5
7. I felt anxious	☐1	☐2	☐3	☐4	☐5
8. I felt tense	☐1	☐2	☐3	☐4	☐5

In the past 7 days:	Never	Rarely	Some-times	Often	Always
1. I felt worthless	☐1	☐2	☐3	☐4	☐5
2. I felt helpless	☐1	☐2	☐3	☐4	☐5
3. I felt depressed	☐1	☐2	☐3	☐4	☐5
4. I felt hopeless	☐1	☐2	☐3	☐4	☐5
5. I felt like a failure	☐1	☐2	☐3	☐4	☐5
6. I felt unhappy	☐1	☐2	☐3	☐4	☐5
7. I felt that I had nothing to look forward to	☐1	☐2	☐3	☐4	☐5
8. I felt that nothing could cheer me up	☐1	☐2	☐3	☐4	☐5

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During the past 7 days:	Not at all	A little bit	Some what	Quite a bit	Very Much
1. I felt fatigued	☐1	☐2	☐3	☐4	☐5
2. I had trouble starting things because I was tired	☐1	☐2	☐3	☐4	☐5
In the past 7 days:	**Not at all**	**A little bit**	**Some what**	**Quite a bit**	**Very Much**
3. How run down did you feel on average?	☐1	☐2	☐3	☐4	☐5
4. How fatigued were you on average?	☐1	☐2	☐3	☐4	☐5
5. How much were you bothered by your fatigue on average?	☐1	☐2	☐3	☐4	☐5
6. To what degree did your fatigue interfere with your physical functioning?	☐1	☐2	☐3	☐4	☐5
In the past 7 days:	**Never**	**Rarely**	**Some-times**	**Often**	**Always**
7. How often did you have to push yourself to get things done because of your fatigue?	☐1	☐2	☐3	☐4	☐5
8. How often did you have trouble finishing things because of your fatigue?	☐1	☐2	☐3	☐4	☐5

Are you interested in being contacted about future cancer survivor studies?
__ Yes
__ No

Appendix J. Study Instruments

What time did you wake up this morning? _____

Please rate your current anxiety level:

1	2	3	4	5	6
Relaxed	Mild		Moderate		High

Waist Circumference in Cm _____
Hip Circumference in Cm

Height in cm _____
Weight in kg _____

Any major life events occur in the last week that may have interfered with how you answered the questions on the survey?

Appendix K.Venipuncture standard operating procedures

Appendix K Venipuncture standard operating procedures

Venipuncture Procedure

1. Ascertaining the participant's willingness to have venipuncture performed.
2. Ask or verify which arm is the dominant arm ?
3. Assemble the venipuncture equipment:
    a. Disposable vinyl gloves
    b. Venipuncture needle & holder
    c. Alcohol wipes
    d. Gauze
    e. Collection tube – a red top blood tube.
4. Put on disposable vinyl gloves.
5. Assemble the venipuncture collection kit (connect needle to holder).
6. Palpate the area for a vein.
7. Cleanse the intended insertion site with iodine/betadine swab.
8. Allow the iodine/betadine to dry.
9. Apply a tourniquet at least 2 inches above the venipuncture site.
10. Allow the vein to fill with blood.
11. Wipe off any iodine/betadine with an alcohol swab, allow the alcohol to dry.
12. Insert red top tube into the venipuncture chamber, ready to be pushed onto the needle device – but not pushed on yet.
13. Insert the bevel under the skin and there is a "flash" of blood in the needle, push the red top tube onto the venipuncture needle hub.
14. Advance the needle cautiously into the vein, success will be noted when blood flows into the red top tube.
15. When approximately 4-5 cc are in the red top tube, release the tourniquet.
16. Allow the tube to fill to 15-20 cc.
17. Apply dry gauze to the insertion site while simultaneously withdrawing the needle from the child's arm.
18. Ask the participant to hold the gauze firmly in place while you safely dispose of the needle in the small biohazard needle disposable box.
19. Apply a small bandaid to the insertion site.
20. Label the red top tube with the date, time, and participants ID.
21. Ask the participant how the arm feels, is s/he feeling dizzy, was it uncomfortable.
22. If the they feel dizzy, offer juice, encourage to stay sitting or laying down until dizziness passes.

Appendix L. Millipore Multiplex Protocol

Human High Sensitivity T Cell Magnetic Bead Panel

96-Well Plate Assay

Cat. # HSTCMAG-28SK, HSTCMAG28SPMX13, HSTCMAG28SPMX21, HSTCMAG28PMX13BK, HSTCMAG28PMX21BK

Appendix L. Millipore Multiplex Protocol

MILLIPLEX® MAP

MILLIPLEX® MAP Human High Sensitivity T Cell Magnetic Bead Panel 96-Well Plate Assay

 # HSTCMAG-28SK
 # HSTCMAG28SPMX13
 # HSTCMAG28SPMX21
 # HSTCMAG28PMX13BK
 # HSTCMAG28PMX21BK

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For Research Use Only. Not for Use in Diagnostic Procedures.

By purchasing this product, which contains fluorescently labeled microsphere beads authorized by Luminex Corporation ("Luminex"), you, the customer, acquire the right under Luminex's patent rights, if any, to use this product or any portion of this product, including without limitation the microsphere beads contained herein, only with Luminex's laser based fluorescent analytical test instrumentation marketed under the name of Luminex 100™ IS, 200™, HTS, FLEXMAP 3D®, MAGPIX®.

Appendix L. Millipore Multiplex Protocol

Human High Sensitivity T Cell Magnetic Bead Panel

INTRODUCTION

Cytokines are immunomodulatory polypeptides that play key roles in both adaptive and innate immune responses. A generic term, "cytokines" includes myokines (produced by mononuclear phagocytic cells), lymphokines (produced by activated Th cells), interleukins (acting as mediators between T cells) and chemokines (responsible for T-cell migration). One of the regulatory mechanisms of the immune system, cytokines act at the recognition, activation, or effector phases of an immune response, modulating the development and functional activities of the subtypes of T cells, B cells and myeloid cells. Consequently, research involving cytokines plays a significant role in achieving a deeper understanding of the immune system and its multi-faceted response to most antigens, especially those responses that make up the inflammatory process.

Low levels of inflammation are involved in many clinical and sub-clinical disease states, such as autoimmune disease, cardiovascular disease, diabetes, neurological disorders and cancer. Measuring picogram levels of cytokines, therefore, is critical for understanding the pathogenesis of these diseases.

MILLIPLEX® MAP offers the broadest selection of analytes across a wide range of disease states and species. Once the analytes of interest have been identified, you can rely on the quality that we build into each kit to produce results you can trust. In addition to the assay characteristics listed in the protocol, other performance criteria evaluated during the validation process include: cross-reactivity, dilution linearity, kit stability, and sample behavior (e.g. detectability and stability).

Each MILLIPLEX® MAP panel and kit includes:

- Quality controls (QCs) provided to qualify assay performance
- Comparison of standard (calibrator) and QC lots to a reference lot to ensure lot-to-lot consistency
- Optimized serum matrix to mimic native analyte environment
- Detection antibody cocktails designed to yield consistent analyte profiles within panel

In addition each panel and kit meets stringent manufacturing criteria to ensure batch-to-batch reproducibility. The MILLIPLEX® MAP Human High Sensitivity T Cell Magnetic Bead Panel thus enables you to focus on the therapeutic potential of cytokines as well as the modulation of even low levels of cytokine expression. Coupled with the Luminex xMAP® platform in a magnetic bead format, you receive the advantage of ideal speed and sensitivity, allowing quantitative multiplex detection of dozens of analytes simultaneously, which can dramatically improve productivity.

EMD Millipore's MILLIPLEX® MAP Human High Sensitivity T Cell Magnetic Bead Panel is part of the most versatile system available for cytokines research. From our single to multiplex biomarker solutions, we partner with you to design, develop, analytically validate and build the most comprehensive library available for protein detection and quantitation.

- MILLIPLEX® MAP offers you:
    - The ability to select a 13-plex or 21-plex pre-mixed kit
    - The ability to choose any combination of analytes from our panel of 21 analytes to design a custom kit that better meets your needs.
    - A convenient "all-in-one" box format that gives you the assurance that you will have all the necessary reagents you need to run your assay.

In addition data obtained from the High Sensitivity T Cell Panel will correlate with data for the respective cytokines in the Human Cytokine/Chemokine Panels I, II and III, furthering your ability to measure specific cytokine response in both normal and disease states.

Appendix L. Millipore Multiplex Protocol

EMD Millipore's MILLIPLEX® MAP Human High Sensitivity T Cell Magnetic Bead Panel is to be used for the simultaneous quantification of any or all of the following analytes in human plasma, serum, and cell/tissue culture supernatant samples: Fractalkine, GM-CSF, IFNγ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p70), IL-13, IL-17A, IL-21, IL-23, ITAC, MIP-1α, MIP-1β, MIP-3α and TNFα.

For Research Use Only. Not for Use in Diagnostic Procedures.

Please read entire protocol before use.

It is important to use same assay incubation conditions throughout your study.

PRINCIPLE

MILLIPLEX® MAP is based on the Luminex xMAP® technology — one of the fastest growing and most respected multiplex technologies offering applications throughout the life-sciences and capable of performing a variety of bioassays including immunoassays on the surface of fluorescent-coded magnetic beads known as MagPlex®-C microspheres.

- Luminex uses proprietary techniques to internally color-code microspheres with two fluorescent dyes. Through precise concentrations of these dyes, distinctly colored bead sets of 500 5.6 µm polystyrene microspheres or 80 6.45 µm magnetic microspheres can be created, each of which is coated with a specific capture antibody.
- After an analyte from a test sample is captured by the bead, a biotinylated detection antibody is introduced.
- The reaction mixture is then incubated with Streptavidin-PE conjugate, the reporter molecule, to complete the reaction on the surface of each microsphere.
- EMD Millipore provides three Luminex instruments to acquire and analyze data using two detection methods:
    - The Luminex analyzers Luminex 200™ and FLEXMAP 3D®, flow cytometry-based instruments that integrate key xMAP® detection components, such as lasers, optics, advanced fluidics and high-speed digital signal processors.
    - The Luminex analyzer (MAGPIX®), a CCD-based instrument that integrates key xMAP® capture and detection components with the speed and efficiency of magnetic beads.
- Each individual microsphere is identified and the result of its bioassay is quantified based on fluorescent reporter signals. EMD Millipore combines the streamlined data acquisition power of Luminex xPONENT® acquisition software with sophisticated analysis capabilities of the new MILLIPLEX® Analyst 5.1, integrating data acquisition and analysis seamlessly with all Luminex instruments.

The capability of adding multiple conjugated beads to each sample results in the ability to obtain multiple results from each sample. Open-architecture xMAP® technology enables multiplexing of many types of bioassays reducing time, labor and costs over traditional methods.

Appendix L. Millipore Multiplex Protocol

STORAGE CONDITIONS UPON RECEIPT

- Recommended storage for kit components is 2 - 8°C.
- For long-term storage, freeze reconstituted standards and controls at ≤ -20°C. Avoid multiple (>2) freeze/thaw cycles.
- **DO NOT FREEZE Antibody-Immobilized Beads, Detection Antibody, and Streptavidin-Phycoerythrin**.

REAGENTS SUPPLIED

Note: Store all reagents at 2 – 8°C

Reagents Supplied	Catalog Number	Volume	Quantity
Human High Sensitivity T Cell Standard	HSTC-8028	Lyophilized	1 vial
Human High Sensitivity T Cell Quality Controls 1 and 2	HSTC-6028	Lyophilized	2 vials
Serum Matrix Note: Contains 0.08% Sodium Azide	MXHSM-7	Lyophilized	1 vial
Set of one 96-Well Plate with 2 sealers	----------	----------	1 plate 2 sealers
Assay Buffer	L-ABIR	15 mL	1 bottle
10X Wash Buffer Note: Contains 0.05% Proclin	L-WB	60 mL	1 bottle
Human High Sensitivity T Cell Detection Antibodies	HSTC-1028	5.5 mL	1 bottle
Streptavidin-Phycoerythrin	MC-SAPE7	5.5 mL	1 bottle
Bead Diluent	LBD	3.5 mL	1 bottle
Mixing Bottle (not provided with premixed panel)	----------	----------	1 bottle

Human High Sensitivity T Cell Antibody-Immobilized Premixed Magnetic Beads:

Premixed 13-plex Beads	HSTCPMX13-MAG	3.5 mL	1 bottle
Premixed 21-plex Beads	HSTCPMX21-MAG	3.5 mL	1 bottle

Included Human High Sensitivity T Cell Antibody-Immobilized Magnetic Beads are dependent on customizable selection of analytes within the panel (see next page).

Appendix L. Millipore Multiplex Protocol

REAGENTS SUPPLIED (continued)

Human High Sensitivity T Cell Antibody-Immobilized Magnetic Beads:

Bead/Analyte Name	Luminex Magnetic Bead Region	Customizable **21** Analytes (**50**X concentration, **90** µL) Available	Cat. #	**13**-Plex Magnetic Premixed Beads	**21**-Plex Magnetic Premixed Beads
Anti-Human ITAC Beads	19	✓	HITAC-MAG		✓
Anti-Human GM-CSF Beads	20	✓	HGMCSF-MAG	✓	✓
Anti-Human Fractalkine Beads	21	✓	HFKN-MAG		✓
Anti-Human IFNγ Beads	25	✓	HCYIFNG-MAG	✓	✓
Anti-Human IL-10 Beads	27	✓	HCYIL10-MAG	✓	✓
Anti-Human MIP-3α Beads	28	✓	HMIP3A-MAG		✓
Anti-Human IL-12 (p70) Beads	33	✓	HIL12P70-MAG	✓	✓
Anti-Human IL-13 Beads	35	✓	HIL13-MAG	✓	✓
Anti-Human IL-17A Beads	39	✓	HIL17-MAG		✓
Anti-Human IL-1β Bead	46	✓	HCYIL1B-MAG	✓	✓
Anti-Human IL-2 Beads	48	✓	HIL2-MAG	✓	✓
Anti-Human IL-21 Beads	52	✓	HIL21-MAG		✓
Anti-Human IL-4 Beads	53	✓	HIL4-MAG	✓	✓
Anti-Human IL-23 Beads	54	✓	HIL23-MAG		✓
Anti-Human IL-5 Beads	55	✓	HIL5-MAG	✓	✓
Anti-Human IL-6 Beads	57	✓	HCYIL6-MAG	✓	✓
Anti-Human IL-7 Beads	61	✓	HIL7-MAG	✓	✓
Anti-Human IL-8 Beads	63	✓	HCYIL8-MAG	✓	✓
Anti-Human MIP-1α	72	✓	HMIP1A-MAG		✓
Anti-Human MIP-1β	73	✓	HMIP1B-MAG		✓
Anti-Human TNFα Beads	75	✓	HCYTNFA-MAG	✓	✓

Appendix L. Millipore Multiplex Protocol

MATERIALS REQUIRED BUT NOT PROVIDED

Reagents

1. Luminex Sheath Fluid (EMD Millipore Catalog # SHEATHFLUID) or Luminex Drive Fluid (EMD Millipore Catalog # MPXDF-4PK)

Instrumentation / Materials

1. Adjustable Pipettes with Tips capable of delivering 25 µL to 1000 µL
2. Multichannel Pipettes capable of delivering 5 µL to 50 µL or 25 µL to 200 µL
3. Reagent Reservoirs
4. Polypropylene Microfuge Tubes
5. Rubber Bands
6. Aluminum Foil
7. Absorbent Pads
8. Laboratory Vortex Mixer
9. Sonicator (Branson Ultrasonic Cleaner Model # B200 or equivalent)
10. Titer Plate Shaker (VWR® Microplate Shaker Cat # 12620-926 or equivalent)
11. Luminex 200™, HTS, FLEXMAP 3D®, or MAGPIX® with xPONENT® software by Luminex Corporation
12. Automatic Plate Washer for magnetic beads (BioTek® 405 LS and 405 TS, EMD Millipore Catalog # 40-094, # 40-095, # 40-096, # 40-097 or equivalent) or Handheld Magnetic Separation Block (EMD Millipore Catalog # 40-285 or equivalent).

Note: If a plate washer or handheld magnetic separation block for magnetic beads is not available, one can use a microtiter filter plate (EMD Millipore Catalog # MX-PLATE) to run the assay using a Vacuum Filtration Unit (EMD Millipore Vacuum Manifold Catalog # MSVMHTS00 or equivalent with EMD Millipore Vacuum Pump Catalog # WP6111560 or equivalent).

SAFETY PRECAUTIONS

- All blood components and biological materials should be handled as potentially hazardous. Follow universal precautions as established by the Centers for Disease Control and Prevention and by the Occupational Safety and Health Administration when handling and disposing of infectious agents.

- Sodium Azide or Proclin has been added to some reagents as a preservative. Although the concentrations are low, Sodium Azide and Proclin may react with lead and copper plumbing to form highly explosive metal azides. Dispose of unused contents and waste in accordance with international, federal, state, and local regulations.

Note: See Full Labels of Hazardous components on next page.

Appendix L. Millipore Multiplex Protocol

Full Labels of Hazardous Components

Ingredient, Cat #		Full Label	
Human High Sensitivity T Cell Detect Antibodies	HSTC-1028		**Warning.** Causes serious eye irritation. IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
Human High Sensitivity T Cell Quality Control 1 & 2	HSTC-6028		**Danger.** Harmful if swallowed. Causes serious eye damage. Harmful to aquatic life with long lasting effects. Avoid release to the environment. Wear eye protection. IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Get medical advice/ attention.
Human High Sensitivity T Cell Standard	HSTC-8028		**Danger.** Harmful if swallowed. Causes serious eye damage. Harmful to aquatic life with long lasting effects. Avoid release to the environment. Wear eye protection. IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Get medical advice/ attention.
Assay Buffer MILLIPLEX	L-ABIR		**Warning.** Causes serious eye irritation. IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
Streptavidin-Phycoerythrin	MC-SAPE7		**Warning.** Causes serious eye irritation. IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
10X Wash Buffer - MILLIPLEX	L-WB		**Warning.** May cause an allergic skin reaction. Wear protective gloves. IF ON SKIN: Wash with plenty of soap and water.
Serum Matrix	MXHSM-7	No Symbol Required	Harmful to aquatic life with long lasting effects. Avoid release to the environment.

Appendix L. Millipore Multiplex Protocol

UNIQUE FEATURES OF THE HUMAN HIGH SENSITIVITY T CELL MAGNETIC BEAD PANEL

Please read this protocol with care as there are several distinctive steps as summarized below:

- When testing serum or plasma samples, the Standard and the Quality Control vials are reconstituted in Serum Matrix.
    - Both the reconstituted Quality Controls and the Standards are further diluted in Serum Matrix to make the final solutions.
    - Serum Matrix is reconstituted to a final volume of 4 mL.
    - Serum Matrix is used for the background wells.

- When testing tissue culture or other supernatant, the Quality Control and the Standard Vials should be reconstituted and further diluted in the appropriate control culture medium, which will also be used for the background wells.

- 50 µL background, Standard and Quality Controls are added to their appropriate wells on the assay plate.

- 25 µL Sample and 25 µL Assay Buffer are added to the sample wells resulting in a two-fold sample dilution.

- For Quality Control analysis, analyte concentrations DO NOT NEED to be multiplied by the dilution factor.

- Serum or plasma samples with high analyte values may be further diluted in serum matrix prior to the addition of 25 µL to the sample wells.

Appendix L. Millipore Multiplex Protocol

TECHNICAL GUIDELINES

To obtain reliable and reproducible results, the operator should carefully read this entire manual and fully understand all aspects of each assay step before running the assay. The following notes should be reviewed and understood before the assay is set up.

- FOR RESEARCH USE ONLY. NOT FOR USE IN DIAGNOSTIC PROCEDURES.
- Do not use beyond the expiration date on the label.
- Do not mix or substitute reagents with those from other lots or sources.
- The Antibody-Immobilized Beads are light sensitive and must be protected from light at all times. Cover the assay plate containing beads with opaque plate lid or aluminum foil during all incubation steps.
- It is important to allow all reagents to warm to room temperature (20-25°C) before use in the assay.
- Incomplete washing can adversely affect the assay outcome. All washing must be performed with the Wash Buffer provided.
- The standards prepared by serial dilution must be used within 1 hour of preparation. Discard any unused standards except the standard stock which may be stored at ≤ -20°C for 1 month and at ≤ -80°C for greater than one month.
- If samples fall outside the dynamic range of the assay, further dilute the samples two-fold with the appropriate diluent and repeat the assay.
- Any unused mixed Antibody-Immobilized Beads may be stored in the Mixing Bottle at 2-8°C for up to **one month.**
- During the preparation of the standard curve, make certain to mix the higher concentration well before making the next dilution. Use a new tip with each dilution.
- The plate should be read immediately after the assay is finished. If, however, the plate cannot be read immediately, seal the plate, cover with aluminum foil or an opaque lid, and store the plate at 2-8°C for up to 24 hours. Prior to reading, agitate the plate on the plate shaker at room temperature for 10 minutes. Delay in reading a plate may result in decreased sensitivity for some analytes.
- The titer plate shaker should be set at a speed to provide maximum orbital mixing without splashing of liquid outside the wells. For the recommended plate shaker, this would be a setting of 5-7 which is approximately 500-800 rpm.
- Ensure that the needle probe is clean. This may be achieved by sonication and/or alcohol flushes.
- When reading the assay on Luminex 200™, adjust probe height according to the protocols recommended by Luminex to the kit solid plate or to the recommended EMD Millipore filter plates using 3 alignment discs. When reading the assay on MAGPIX®, adjust probe height according to the protocols recommended by Luminex to the kit solid plate or to the recommended EMD Millipore filter plates using 2 alignment discs. When reading the assay on FLEXMAP 3D®, adjust probe height according to the protocols recommended by Luminex to the kit solid plate using 1 alignment disc.

  For FLEXMAP 3D® when using the solid plate in the kit, the final resuspension should be with 150 µL Sheath Fluid in each well and 75 µL should be aspirated.
- For cell culture supernatants or tissue extraction, use the culture or extraction medium as the matrix solution in background and for reconstitution of standard curve and controls.

Appendix L. Millipore Multiplex Protocol

TECHNICAL GUIDELINES (continued)

- For serum/plasma samples that require dilution, use the **MXHSM-7** provided and prepared as described in the kit for a two-fold dilution (e.g. 50 µL of sample and 50 µL of MXHSM-7).
- For cell/tissue homogenate, the final cell or tissue homogenate should be prepared in a buffer that has a neutral pH, contains minimal detergents or strong denaturing detergents, and has an ionic strength close to physiological concentration. Avoid debris, lipids, and cell/tissue aggregates. Centrifuge samples before use.
- Vortex all reagents well before adding to plate.

SAMPLE COLLECTION AND STORAGE

A. Preparation of Serum Samples:
   - Allow the blood to clot for at least 30 minutes before centrifugation for 10 minutes at 1000xg. Remove serum and assay immediately or aliquot and store samples at ≤ -20°C.
   - Avoid multiple **(>2)** freeze/thaw cycles.
   - When using frozen samples, it is recommended to thaw the samples completely, mix well by vortexing and centrifuge prior to use in the assay to remove particulates.
   - Neat Serum samples are used. If further dilution is required, we recommend diluting samples no more than one to two in MXHSM-7 (e.g. 50 µL sample and 50 µL MXHSM-7).

B. Preparation of Plasma Samples:
   - Plasma collection using EDTA as an anti-coagulant is recommended. Centrifuge for 10 minutes at 1000xg within 30 minutes of blood collection. Remove plasma and assay immediately or aliquot and store samples at ≤ -20°C.
   - Avoid multiple (>2) freeze/thaw cycles.
   - When using frozen samples, it is recommended to thaw the samples completely, mix well by vortexing and centrifuge prior to use in the assay to remove particulates.
   - Neat Plasma samples are used. If further dilution is required, we recommend diluting samples no more than one to two in MXHSM-7 (e.g. 50 µL sample and 50 µL MXHSM-7).

C. Preparation of Tissue Culture Supernatant:
   - Centrifuge the sample to remove debris and assay immediately or aliquot and store samples at ≤ -20°C.
   - Avoid multiple (>2) freeze/thaw cycles.
   - Tissue culture supernatant may require a dilution with an appropriate control medium prior to assay. Tissue/cell extracts should be done in neutral buffers containing reagents and conditions that do not interfere with assay performance. Excess concentrations of detergent, salt, denaturants, high or low pH, etc. will negatively affect the assay. Organic solvents should be avoided. The tissue/cell extract samples should be free of particles such as cells or tissue debris.

Appendix L. Millipore Multiplex Protocol

SAMPLE COLLECTION AND STORAGE (continued)

NOTE:

- A maximum of **25 µL** per well of neat or one to two diluted serum or plasma can be used. Tissue culture or other media may also be used.
- All samples must be stored in polypropylene tubes. **DO NOT STORE SAMPLES IN GLASS.**
- Avoid debris, lipids and cells when using samples with gross hemolysis or lipemia.
- Care must be taken when using heparin as an anti-coagulant since an excess of heparin will provide falsely high values. Use no more than 10 IU heparin per mL of blood collected.

PREPARATION OF REAGENTS FOR IMMUNOASSAY

A. Preparation of Antibody-Immobilized Beads

If premixed beads are used, sonicate the premixed bead bottle 30 seconds and then vortex for 1 minute before use.

For individual vials of beads, sonicate each antibody-bead vial for 30 seconds; vortex for 1 minute. Add 70 µL from each antibody-bead vial to the Mixing Bottle and bring final volume to 3.5 mL with LBD. Vortex the mixed beads well. Unused portion may be stored at 2-8°C for up to one month. (Note: Due to the composition of magnetic beads, you may notice a slight color in the bead solution. This does not affect the performance of the beads or the kit.)

Example: When using 10 antibody-immobilized beads, add 70 µL from each of the 10 bead vials to the Mixing Bottle. Then add 2.8 mL LBD

B. Preparation of Serum Matrix

This step is required for serum or plasma samples only.

Add 1.0 mL deionized water to the bottle containing lyophilized serum matrix (Cat# MXHSM-7). Mix well. Allow at least 10 minutes for complete reconstitution. Add 3 mL Assay Buffer (Cat# L-ABIR) to the bottle for a final volume of 4 mL. Unused reconstituted matrix should be stored at ≤ -20°C for up to one month.

C. Preparation of Quality Controls

For serum and plasma samples, reconstitute Quality Control 1 (QC1) and Quality Control 2 (QC2) vials with **250 µL MXHSM-7**. **These are the Stock QC Vials.** Invert the Stock Vials several times to mix and vortex. Allow the vials to sit for 5-10 minutes. Label two tubes QC1 and QC2 and add 150 µL MXHSM-7 to each tube. Remove 50 µL from QC1 or QC2 Stock Vials and add to the 150 µL MXHSM-7 in the respective QC1 and QC2 tubes and vortex. **Use these one to four diluted QCs in the assay**. Unused portions may be stored at ≤ -20°C for up to one month.

For culture samples, substitute the appropriate sample media for the MXHSM-7 used for serum and plasma samples above.

Appendix L. Millipore Multiplex Protocol

PREPARATION OF REAGENTS FOR IMMUNOASSAY (continued)

D. Preparation of Wash Buffer

Bring the 10X Wash Buffer to room temperature and mix to bring all salts into solution. Dilute 60 mL of 10X Wash Buffer with 540 mL deionized water. Store the unused portion at 2-8°C for up to one month.

E. Preparation of Human High Sensitivity T Cell Standard

1.) For serum and plasma samples, reconstitute the Human High Sensitivity T Cell Standard with **250 µL MXHSM-7**. Invert the vial several times to mix. Vortex the vial for 10 seconds. Allow the vial to sit for 5-10 minutes. **This is the Stock Standard Vial NOT Standard 7.** Unused Standard may be stored at ≤ -20°C for up to one month.

2). Preparation of Working Standards

For serum and plasma samples, label seven polypropylene microfuge tubes as Standard 7, Standard 6, Standard 5, Standard 4, Standard 3, Standard 2 and Standard 1. Add 150 µL of MXHSM-7 to each of the seven tubes. Prepare serial dilutions by adding 50 µL of the Stock Standard to the Standard 7 tube, mix well and transfer 50 µL of the Standard 7 to the Standard 6 tube, mix well and transfer 50 µL of the Standard 6 tube to the Standard 5 tube, mix well and transfer 50 µL of the Standard 5 tube to the Standard 4 tube, mix well and transfer 50 µL of the Standard 4 tube to the Standard 3 tube, mix well and transfer 50 µL of the Standard 3 tube to the Standard 2 tube, mix well and transfer 50 µL of the Standard 2 tube to the Standard 1 tube and mix well. The 0 pg/mL standard (Background) will be MXHSM-7 or appropriate sample media.

Standard #	Volume of MXHSM-7 to Add	Volume of Standard to Add
Stock Standard	250 µL	0

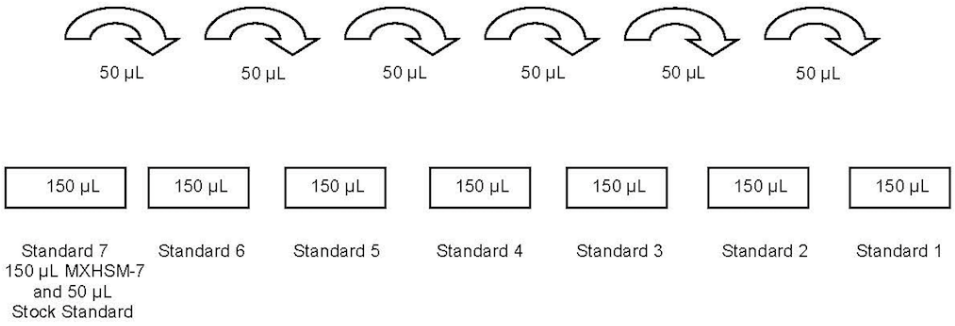
Standard #	Volume of MXHSM-7 to Add	Volume of Standard to Add
Standard 7	150 µL	50 µL of Stock Standard
Standard 6	150 µL	50 µL of Standard 7
Standard 5	150 µL	50 µL of Standard 6
Standard 4	150 µL	50 µL of Standard 5
Standard 3	150 µL	50 µL of Standard 4
Standard 2	150 µL	50 µL of Standard 3
Standard 1	150 µL	50 µL of Standard 2

3). For other samples (tissue culture, cell culture etc.) substitute the appropriate media for the MXHSM-7 used for serum and plasma samples above.

Appendix L. Millipore Multiplex Protocol

PREPARATION OF REAGENTS FOR IMMUNOASSAY (continued)

Preparation of Standards



Standard	ITAC, IL-10 (pg/mL)	GM-CSF (pg/mL)	Fractalkine (pg/mL)	IFNγ, MIP-3α (pg/mL)
Standard 1	1.46	1.22	18.3	0.61
Standard 2	5.86	4.88	73.2	2.44
Standard 3	23.4	19.5	293.0	9.8
Standard 4	93.8	78.1	1,171.9	39
Standard 5	375	312.5	4,687.5	156
Standard 6	1,500	1,250	18,750	625
Standard 7	6,000	5,000	75,000	2,500

Standard	IL-12p70, IL-1β, IL-2, IL-5 (pg/mL)	IL-13, IL-21 (pg/mL)	IL-17A (pg/mL)	IL-4 (pg/mL)	IL-23 (pg/mL)
Standard 1	0.49	0.24	0.73	1.83	7.93
Standard 2	1.95	0.98	2.93	7.32	31.7
Standard 3	7.81	3.91	11.7	29.3	127.0
Standard 4	31.3	15.63	46.9	117.2	507.8
Standard 5	125	62.5	187.5	468.8	2,031.3
Standard 6	500	250	750	1,875	8,125
Standard 7	2,000	1,000	3,000	7,500	32,500

Appendix L. Millipore Multiplex Protocol

PREPARATION OF REAGENTS FOR IMMUNOASSAY (continued)

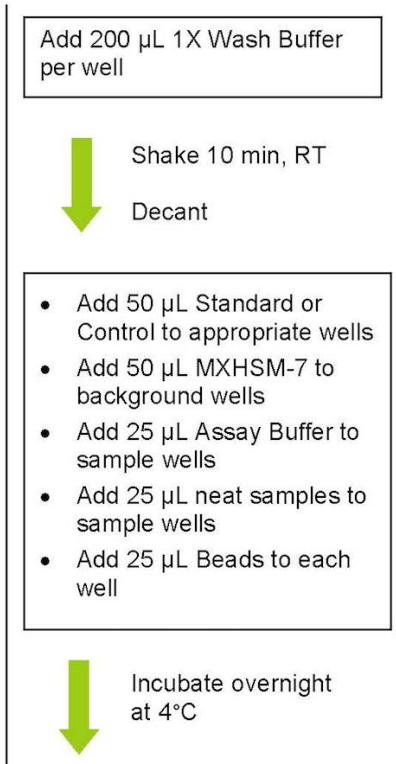
Standard	IL-6 (pg/mL)	IL-7 (pg/mL)	IL-8, MIP-1α (pg/mL)	MIP-1β (pg/mL)	TNFα (pg/mL)
Standard 1	0.18	0.37	0.31	0.92	0.43
Standard 2	0.73	1.46	1.22	3.66	1.71
Standard 3	2.93	5.86	4.88	14.7	6.84
Standard 4	11.7	23.4	19.5	58.6	27.3
Standard 5	46.9	93.8	78.1	234.4	109.4
Standard 6	187.5	375	312.5	937.5	437.5
Standard 7	750	1,500	1,250	3,750	1,750

Appendix L. Millipore Multiplex Protocol

IMMUNOASSAY PROCEDURE

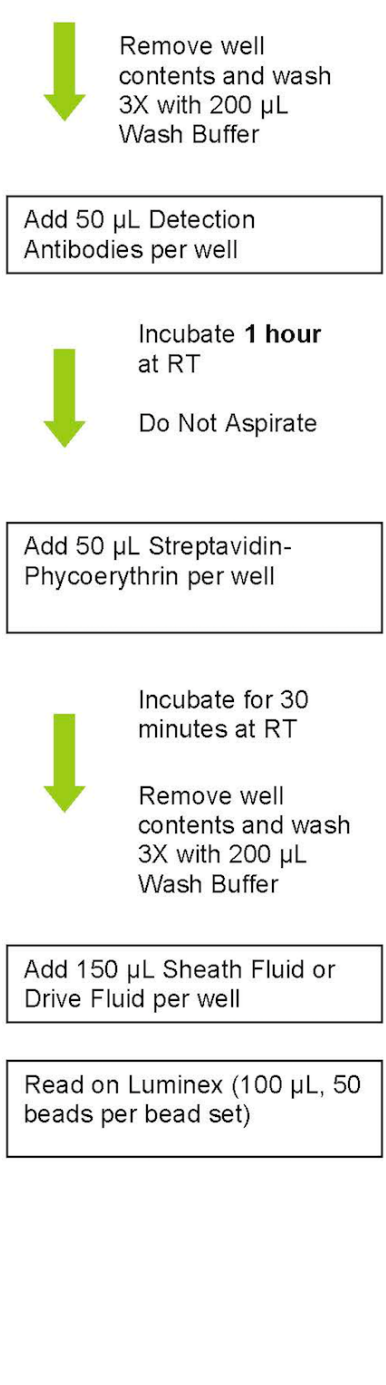
- Prior to beginning this assay, it is imperative to read this protocol completely and to thoroughly understand the Technical Guidelines.
- Allow all reagents to warm to room temperature (20-25°C) before use in the assay.
- Diagram the placement of Standards [0 (Background), standards 1 through 7], Controls 1 and 2, and Samples on Well Map Worksheet in a vertical configuration. (Note: Most instruments will only read the 96-well plate vertically by default.) It is recommended to run the assay in duplicate.
- If using a filter plate, set the filter plate on a plate holder at all times during reagent dispensing and incubation steps so that the bottom of the plate does not touch any surface.

1. Add 200 µL of Wash Buffer into each well of the plate. Seal and mix on a plate shaker for 10 minutes at room temperature (20-25°C).
2. Decant Wash Buffer and remove the residual amount from all wells by inverting the plate and tapping it smartly onto absorbent towels several times.
3. Add 50 µL of each **diluted** Standard or Quality Control into the appropriate wells (**NOT from Stock Vials)**. The **Serum Matrix** should be used for 0 pg/mL standard (background). When assaying tissue culture or other supernatant, use appropriate control culture medium as the background.
4. Add 25 µL of Assay Buffer to the sample wells.
5. Add 25 µL of sample into the sample wells.
6. Vortex Mixing Bottle and add 25 µL of the Mixed or Premixed Beads to each well. (Note: During addition of Beads, shake bead bottle intermittently to avoid settling.)
7. Seal the plate with a plate sealer. Wrap the plate with foil and incubate with agitation on a plate shaker overnight (16-18 hrs) at 4°C



Appendix L. Millipore Multiplex Protocol

8. Gently remove well contents and wash plate 3 times following instructions listed in the **PLATE WASHING** section.
9. Add 50 µL of Detection Antibodies into each well. (Note: Allow the Detection Antibodies to warm to room temperature prior to addition.)
10. Seal, cover with foil and incubate with agitation on a plate shaker for 1 hour at room temperature (20-25°C). **DO NOT ASPIRATE AFTER INCUBATION.**
11. Add 50 µL Streptavidin-Phycoerythrin to each well containing the 50 µL of Detection Antibodies.
12. Seal, cover with foil and incubate with agitation on a plate shaker for 30 minutes at room temperature (20-25°C).
13. Gently remove well contents and wash plate 3 times following instructions listed in the **PLATE WASHING** section.
14. Add 150 µL of Sheath Fluid (or Drive Fluid if using MAGPIX®) to all wells. Resuspend the beads on a plate shaker for 5 minutes.
15. Run plate on Luminex 200™, HTS, FLEXMAP 3D® or MAGPIX® with xPONENT® software.
16. Save and analyze the Median Fluorescent Intensity (MFI) data using a 5-parameter logistic or spline curve-fitting method for calculating analyte concentrations in samples and Controls. **(Note: Because of the built-in two-fold sample dilution, for all neat samples, multiply the calculated concentrations by two. For two-fold diluted samples, multiply the calculated concentrations by four. Calculated Quality Control concentrations do not require multiplication by a dilution factor.)**



Appendix L. Millipore Multiplex Protocol

PLATE WASHING

1.) Solid Plate

If using a solid plate, use either a handheld magnet or magnetic plate washer.

A.) Handheld magnet (EMD Millipore Catalog # 40-285) - Rest plate on magnet for 60 seconds to allow complete settling of magnetic beads. Remove well contents by gently decanting the plate in an appropriate waste receptacle and gently tapping on absorbent pads to remove residual liquid. Wash plate with 200 µL of Wash Buffer by removing plate from magnet, adding Wash Buffer, shaking for 30 seconds, reattaching to magnet, letting beads settle for 60 seconds and removing well contents as previously described after each wash. Repeat wash steps as recommended in Assay Procedure.

B.) Magnetic plate washer (EMD Millipore Catalog # 40-094, # 40-095, # 40-096 and # 40-097) - Please refer to specific automatic plate washer manual for appropriate equipment settings. Please note that after the final aspiration, there will be approximately 25 µL of residual wash buffer in each well. This is expected when using the BioTek plate washer and this volume does not need to be aspirated from the plate.

If using an automatic plate washer other than BioTek® 405 LS or 405 TS, please refer to the manufacturer's recommendations for programming instructions.

2.) Filter Plate (EMD Millipore Catalog # MX-PLATE)

If using a filter plate, use a vacuum filtration manifold to remove well contents. Wash plate with 200 µL/well of Wash Buffer, removing Wash Buffer by vacuum filtration after each wash. Repeat wash steps as recommended in the Assay Procedure.

EQUIPMENT SETTINGS

Luminex 200™, HTS, FLEXMAP 3D®, and MAGPIX® with xPONENT® software:

These specifications are for the Luminex 200™, Luminex HTS, Luminex FLEXMAP 3D®, and Luminex MAGPIX® with xPONENT® software. Luminex instruments with other software (e.g. MasterPlex®, StarStation, LiquiChip, Bio-Plex Manager™, LABScan™100) would need to follow instrument instructions for gate settings and additional specifications from the vendors for reading Luminex magnetic beads.

For magnetic bead assays, the Luminex 200™ and HTS instruments must be calibrated with the xPONENT® 3.1 compatible Calibration Kit (EMD Millipore Catalog # 40-275) and performance verified with the Performance Verification Kit (EMD Millipore Catalog # 40-276). The Luminex FLEXMAP 3D® instrument must be calibrated with the FLEXMAP 3D® Calibrator Kit (EMD Millipore Catalog # 40-028) and performance verified with the FLEXMAP 3D® Performance Verification Kit (EMD Millipore Catalog # 40-029). The Luminex MAGPIX® instrument must be calibrated with the MAGPIX® Calibration Kit (EMD Millipore Catalog # 40-049) and performance verified with the MAGPIX® Performance Verification Kit (EMD Millipore Catalog # 40-050).

NOTE: When setting up a Protocol using the xPONENT® software, you must select MagPlex as the Bead Type in the Acquisition settings.

NOTE: These assays cannot be run on any instruments using Luminex IS 2.3 or Luminex 1.7 software.

Appendix L. Millipore Multiplex Protocol

EQUIPMENT SETTINGS (continued)

The Luminex probe height must be adjusted to the plate provided in the kit. Please use Catalog # MAG-PLATE, if additional plates are required for this purpose.

Events:	50, per bead	
Sample Size:	100 µL	
Gate Settings:	8,000 to 15,000	
Reporter Gain:	Default (low PMT)	
Time Out:	60 seconds	
Bead Set:	Customizable 21-Plex Beads	
	ITAC	19
	GM-CSF	20
	Fractalkine	21
	IFNγ	25
	IL-10	27
	MIP-3α	28
	IL-12 (p70)	33
	IL-13	35
	IL-17A	39
	IL-1β	46
	IL-2	48
	IL-21	52
	IL-4	53
	IL-23	54
	IL-5	55
	IL-6	57
	IL-7	61
	IL-8	63
	MIP-1α	72
	MIP-1β	73
	TNFα	75

QUALITY CONTROLS

The ranges for each analyte in Quality Control 1 and 2 are provided on the card insert or can be located at the EMD MILLIPORE website www.emdmillipore.com using the catalog number as the keyword.

Appendix L. Millipore Multiplex Protocol

ASSAY CHARACTERISTICS

Cross-Reactivity

There was no or negligible cross-reactivity between the antibodies for an analyte and any of the other analytes in this panel.

Assay Sensitivities (minimum detectable concentrations (pg/mL)

Minimum Detectable Concentration (MinDC) is calculated using MILLIPLEX® Analyst 5.1. It measures the true limits of detection for an assay by mathematically determining what the empirical MinDC would be if an infinite number of standard concentrations were run for the assay under the same conditions.

Analyte	Overnight Protocol (n = 7 Assays)	
	MinDC (pg/mL)	MinDC+2SD (pg/mL)
ITAC	1.25	1.98
GM-CSF	0.35	0.60
Fractalkine	8.17	12.53
IFNγ	0.48	0.94
IL-10	0.56	0.93
MIP-3α	0.83	1.39
IL-12 (p70)	0.15	0.27
IL-13	0.23	0.34
IL-17A	0.33	0.52
IL-1β	0.14	0.24
IL-2	0.19	0.30
IL-21	0.14	0.20
IL-4	1.12	1.84
IL-23	3.25	5.11
IL-5	0.12	0.22
IL-6	0.11	0.17
IL-7	0.42	0.60
IL-8	0.13	0.25
MIP-1α	0.94	1.28
MIP-1β	0.67	0.98
TNFα	0.16	0.21

Appendix L. Millipore Multiplex Protocol

ASSAY CHARACTERISTICS (continued)

Precision

Intra-assay precision is generated from the mean of the %CV's from 8 reportable results across two different concentrations of analytes in a single assay. Inter-assay precision is generated from the mean of the %CV's across two different concentrations of analytes across 6 different assays.

Analyte	Overnight Protocol	
	Intra-assay %CV	Inter-assay %CV
ITAC	<5%	<15%
GM-CSF	<5%	<15%
Fractalkine	<5%	<15%
IFNγ	<5%	<20%
IL-10	<5%	<20%
MIP-3α	<5%	<20%
IL-12 (p70)	<6%	<15%
IL-13	<5%	<20%
IL-17A	<5%	<20%
IL-1β	<5%	<15%
IL-2	<5%	<15%
IL-21	<5%	<15%
IL-4	<5%	<15%
IL-23	<5%	<20%
IL-5	<5%	<20%
IL-6	<5%	<20%
IL-7	<5%	<15%
IL-8	<5%	<15%
MIP-1α	<5%	<15%
MIP-1β	<5%	<15%
TNFα	<5%	<15%

Appendix L. Millipore Multiplex Protocol

ASSAY CHARACTERISTICS (continued)

Accuracy

Spike Recovery: The data represent mean percent recovery of spiked standards ranging from low, medium, and high concentration in serum matrices (n=4).

Analyte	Overnight Protocol
	% Recovery in Serum Matrix
ITAC	106
GM-CSF	101
Fractalkine	101
IFNγ	101
IL-10	104
MIP-3α	101
IL-12 (p70)	100
IL-13	103
IL-17A	106
IL-1β	98
IL-2	103
IL-21	101
IL-4	103
IL-23	100
IL-5	101
IL-6	107
IL-7	98
IL-8	103
MIP-1α	101
MIP-1β	98
TNFα	103

Appendix L. Millipore Multiplex Protocol

TROUBLESHOOTING GUIDE

Problem	Probable Cause	Solution
Insufficient bead count	Plate washer aspirate height set too low	Adjust aspiration height according to manufacturers' instructions.
	Bead mix prepared inappropriately	Sonicate bead vials and vortex just prior to adding to bead mix bottle according to protocol. Agitate bead mix intermittently in reservoir while pipetting this into the plate.
	Samples cause interference due to particulate matter or viscosity	See above. Also sample probe may need to be cleaned with alcohol flushes, back flushes and washes; or, if needed, probe should be removed and sonicated.
	Probe height not adjusted correctly	When reading the assay on Luminex 200™, adjust probe height to the kit solid plate or to the recommended EMD Millipore filter plates using 3 alignment discs. When reading the assay on MAGPIX®, adjust probe height to the kit solid plate or to the recommended EMD Millipore filter plates using 2 alignment discs. When reading the assay on FLEXMAP 3D®, adjust probe height to the kit solid plate using 1 alignment disc. For FLEXMAP 3D® when using the solid plate in the kit, the final resuspension should be with 150 µL Sheath Fluid in each well and 75 µL should be aspirated.
Background is too high	Background wells were contaminated	Avoid cross-well contamination by using sealer appropriately and pipetting with multichannel pipettes without touching reagent in plate.
	Matrix used has endogenous analyte or interference	Check matrix ingredients for cross-reacting components (e.g. interleukin modified tissue culture medium).
	Insufficient washes	Increase number of washes.
Beads not in region or gate	Luminex instrument not calibrated correctly or recently	Calibrate Luminex instrument based on manufacturer's instructions, at least once a week or if temperature has changed by >3°C.
	Gate settings not adjusted correctly	Some Luminex instruments (e.g. Bio-Plex®) require different gate settings than those described in the kit protocol. Use instrument default settings.
	Wrong bead regions in protocol template	Check kit protocol for correct bead regions or analyte selection.
	Incorrect sample type used	Samples containing organic solvents or if highly viscous should be diluted or dialyzed as required.
	Instrument not washed or primed	Prime the Luminex instrument 4 times to rid it of air bubbles, wash 4 times with sheath fluid or water if there is any remnant alcohol or sanitizing liquid.
	Beads were exposed to light	Keep plate and bead mix covered with dark lid or aluminum foil during all incubation steps.

Appendix L. Millipore Multiplex Protocol

Problem	Probable Cause	Solution
Signal for whole plate is same as background	Incorrect or no Detection Antibody was added	Add appropriate Detection Antibody and continue.
	Streptavidin-Phycoerythrin was not added	Add Streptavidin-Phycoerythrin according to protocol. If Detection Antibody has already been removed, sensitivity may be low.
Low signal for standard curve	Detection Antibody may have been removed prior to adding Streptavidin-Phycoerythrin	May need to repeat assay if desired sensitivity not achieved.
	Incubations done at inappropriate temperatures, timings or agitation.	Assay conditions need to be checked.
Signals too high, standard curves are saturated	Calibration target value set too high	With some Luminex instruments (e.g. Bio-Plex®) default target setting for RP1 calibrator is set at high PMT. Use low target value for calibration and reanalyze plate.
	Plate incubation was too long with standard curve and samples	Use shorter incubation time.
Sample readings are out of range	Samples contain no or below detectable levels of analyte	If below detectable levels, it may be possible to use higher sample volume. Check with technical support for appropriate protocol modifications.
	Samples contain analyte concentrations higher than highest standard point	Samples may require dilution and reanalysis for just that particular analyte.
	Standard curve was saturated at higher end of curve	See above.
High variation in samples and/or standards	Multichannel pipette may not be calibrated	Calibrate pipettes.
	Plate washing was not uniform	Confirm all reagents are removed completely in all wash steps.
	Samples may have high particulate matter or other interfering substances	See above.
	Plate agitation was insufficient	Plate should be agitated during all incubation steps using an orbital plate shaker at a speed where beads are in constant motion without causing splashing.
	Cross-well contamination	Check when reusing plate sealer that no reagent has touched sealer. Care should be taken when using same pipette tips that are used for reagent additions and that pipette tip does not touch reagent in plate.

Appendix L. Millipore Multiplex Protocol

Appendix L Millipore Multiplex Protocol

FOR FILTER PLATES ONLY		
Problem	**Probable Cause**	**Solution**
Filter plate will not vacuum	Vacuum pressure is insufficient	Increase vacuum pressure such that 0.2 mL buffer can be suctioned in 3-5 seconds.
	Samples have insoluble particles	Centrifuge samples just prior to assay set-up and use supernatant.
	High lipid concentration	After centrifugation, remove lipid layer and use supernatant.
Plate leaked	Vacuum pressure too high	Adjust vacuum pressure such that 0.2 mL buffer can be suctioned in 3-5 seconds. May need to transfer contents to a new (blocked) plate and continue.
	Plate set directly on table or absorbent towels during incubations or reagent additions	Set plate on plate holder or raised edge so bottom of filter is not touching any surface.
	Insufficient blotting of filter plate bottom causing wicking	Blot the bottom of the filter plate well with absorbent towels after each wash step.
	Pipette touching plate filter during additions	Pipette to the side of plate.
	Probe height not adjusted correctly	Adjust probe to 3 alignment discs in well H6.
	Sample too viscous	May need to dilute sample.

Appendix L. Millipore Multiplex Protocol

REPLACEMENT REAGENTS	Catalog #
Human High Sensitivity T Cell Standard	HSTC-8028
Human High Sensitivity T Cell Quality Controls 1 and 2	HSTC-6028
Serum Matrix	MXHSM-7
Human High Sensitivity T Cell Detection Antibodies	HSTC-1028
Streptavidin-Phycoerythrin	MC-SAPE7
Assay Buffer	L-ABIR
Set of two 96-Well plates with sealers	MAG-PLATE
Bead Diluent	LBD
10X Wash Buffer	L-WB
Human High Sensitivity T Cell 13 Plex Premixed Magnetic Bead Panel – BULK PACKAGED	HSTCMAG28PMX13BK
Human High Sensitivity T Cell 21 Plex Premixed Magnetic Bead Panel – BULK PACKAGED	HSTCMAG28PMX21BK

Antibody-Immobilized Magnetic Beads

Analyte	*Bead #*	*Cat. #*
ITAC	19	HITAC-MAG
GM-CSF	20	HGMCSF-MAG
Fractalkine	21	HFKN-MAG
IFNγ	25	HCYIFNG-MAG
IL-10	27	HCYIL10-MAG
MIP-3α	28	HMIP3A-MAG
IL-12 (p70)	33	HIL12P70-MAG
IL-13	35	HIL13-MAG
IL-17A	39	HIL17-MAG
IL-1β	46	HCYIL1B-MAG
IL-2	48	HIL2-MAG
IL-21	52	HIL21-MAG
IL-4	53	HIL4-MAG
IL-23	54	HIL23-MAG
IL-5	55	HIL5-MAG
IL-6	57	HCYIL6-MAG
IL-7	61	HIL7-MAG
IL-8	63	HCYIL8-MAG
MIP-1α	72	HMIP1A-MAG
MIP-1β	73	HMIP1B-MAG
TNFα	75	HCYTNFA-MAG
Premixed 13-plex Beads		HSTCPMX13-MAG
Premixed 21-plex Beads		HSTCPMX21-MAG

Appendix L. Millipore Multiplex Protocol

ORDERING INFORMATION

To place an order:

To assure the clarity of your custom kit order, please FAX the following information to our customer service department:

Include:

- Your name, telephone and/or fax number
- Customer account number
- Shipping and billing address
- Purchase order number
- Catalog number and description of product
- Quantity of kits
- Selection of MILLIPLEX® Analytes

FAX: (636) 441-8050

Toll-Free US: 1-800-MILLIPORE
781-533-8870

Mail Orders: EMD Millipore Corporation
6 Research Park Drive
St. Charles, Missouri 63304 U.S.A.

For European Customers:

To best serve our European customers in placing an order or obtaining additional information about MILLIPLEX® MAP products, please contact your multiplex specialist or sales representative or email our European Customer Service at:

Austria	AUCustomerService@merckgroup.com
Belgium	BENLCustomerService@merckgroup.com
Denmark	denmark@merckgroup.com
France	FRCustomerService@merckgroup.com
Finland	Asiakaspalvelu@merckgroup.com
Germany	GECustomerService@merckgroup.com
Ireland	IECustomerService@merckgroup.com
Italy	CSR-IT@merckgroup.com
Netherlands	BENLCustomerService@merckgroup.com
Norway	Norway@merckgroup.com
Spain	pedidos@merckgroup.com
Sweden	Kundservice@merckgroup.com
Switzerland	SZCustomerService@merckgroup.com
UK	UKCustomerService@merckgroup.com

Appendix L. Millipore Multiplex Protocol

ORDERING INFORMATION (continued)

Conditions of Sale

For Research Use Only. Not for Use in Diagnostic Procedures.

Material Safety Data Sheets (MSDS)

Material Safety Data Sheets for EMD Millipore products may be ordered by fax or phone or through our website at www.emdmillipore.com/techlibrary/index.do.

Technical Services

http://www.emdmillipore.com/techservices

To contact by phone

For North America: Toll-Free US: 1-(800) 221-1975 or 1-(781) 533-8045

Outside North America, contact your local office
http://www.emdmillipore.com/offices

Appendix L. Millipore Multiplex Protocol

Appendix L Millipore Multiplex Protocol

WELL MAP

	1	2	3	4	5	6	7	8	9	10	11	12
A	0 Standard (Background)	Standard #4	QC-1 Control	Etc.								
B	0 Standard (Background)	Standard #4	QC-1 Control									
C	Standard #1	Standard #5	QC-2 Control									
D	Standard #1	Standard #5	QC-2 Control									
E	Standard #2	Standard #6	Sample 1									
F	Standard #2	Standard #6	Sample 1									
G	Standard #3	Standard #7	Sample 2									
H	Standard #3	Standard #7	Sample 2									

Appendix M. Descriptive statistics and reliability for all the scales and subscales in the sample with incomplete data (N=75)

Appendix M

Study Variable Descriptives on Full Sample Excluding Cytokines (N=75)

Measure	Mean (SD)	Min, Max	Median	Shapiro-Wilk◆	Skewness (std. error)	Kurtosis (std. error)	Cronbach's Alpha
BMI	27.46 (5.59)	18.62, 42.46	25.80	.001	.83(.28)	-0.11(.55)	
HWR	0.81 (.17)	0.62, 1.51	0.78	.001	2.99(.28)	9.69(.55)	
Years Education	16.6 (2.16)	12, 22	16	.001	.07 (.28)	.31(.55)	
PROMIS Anxiety	16.79 (8.36)	8, 40	16	.000	1.11 (.28)	.84 (.55)	.96
PROMIS Depression	13.63 (6.60)	8, 32	11	.000	1.22 (.28)	.57 (.55)	.94
PROMIS Fatigue	21.25 (8.18)	8, 40	20	.030	.46 (.28)	-.47 (.55)	.96
PSS	14.07 (8.42)	0, 33	15	.098	.23 (.28)	-.72 (.55)	.94
UCLA-R	38.20 (1.30)	20, 60	36	.008	.28 (.28)	-.89 (.55)	.95
IPAQ							
Min. Act. Min	968.37 (715.09)	0, 2400	740	.000	.77 (.28)	-.62 (.55)	
Total Sit Min.	3065.4 (1055.91)	0, 5130	2820	.018	.29 (.28)	-.21 (.55)	
PSQI Total	7.55 (4.28)	0, 17	7.0	.075	.40 (.28)	-.64 (.55)	.74
Sleep Quality	0.99 (0.71)	0, 3	1.0	.001	.26 (.28)	-.23 (.55)	
Latency	1.01 (1.12)	0, 3	1.0	001	.62 (.28)	-1.07(.55)	
Duration	.76 (.88)	0, 3	1.0	.001	1.01 (.28)	.59 (.55)	
Efficiency	1.0 (1.23)	0, 3	0.0	.001	0.76 (.28)	-1.10 (.55)	
Disturbance	1.61 (.59)	0, 3	2.0	.001	-.45 (.28)	-.02 (.55)	
Sleepaid	1.21 (1.37)	0, 3	0	.001	.38 (.28)	-1.74 (.55)	
Daytime Dysfunction	.96 (.72)	0, 3	1.0	.001	.28 (.28)	-.37 (.55)	
ESS	6.75 (4.44)	0, 18	6	.001	.72 (.28)	-.44 (.55)	.84
FACT- Cog Total	94.48 (34.97)	19, 147	95	.006	-.41 (.28)	-.77 (.55)	.98
PCI	47.55 (20.97)	3, 79	50	.004	-.37 (.28)	-.88 (.55)	.97
Impact on QOL	10.68 (5.16)	0, 16	12	.001	-.88 (.28)	-.40 (.55)	.95
Others	14.05 (3.12)	3, 16	16	.001	-1.91 (.28)	3.04 (.55)	.90
PCA	22.20 (8.92)	4, 36	21	.027	-.14 (.28)	-.94 (.55)	.93
HVLT Immediate	29.47 (3.86)	18, 36	30	.008	-.65 (.28)	-.06 (.55)	-
HVLT Delayed	10.36 (1.76)	5, 12	11	.001	-1.18 (.28)	.88 (.55)	-
COWAT	40.19 (12.07)	16, 73	39	.122	.5 (.28)	.31 (.55)	-
TMT A	25.01 (9.08)	11.5, 54	24.23	.001	1.15 (.28)	.82 (.55)	
TMT B	55.82 (22.14)	26.53, 179.45	50.64	.001	2.85 (.28)	12.67 (.55)	

Note. BMI= Body Mass Index; HWR= Hip to Waist Ratio; PSS= Perceived Stress Scale; UCLA-R= UCLA Loneliness Scale Revised version 3; IPAQ= International Physical Activity Questionnaire; PSQI= Pittsburgh Sleep Quality Index; ESS= Epsworth Sleepiness Scale; IL-6= Interleukin

Appendix M. Descriptive statistics and reliability for all the scales and subscales in the sample with incomplete data (N=75)

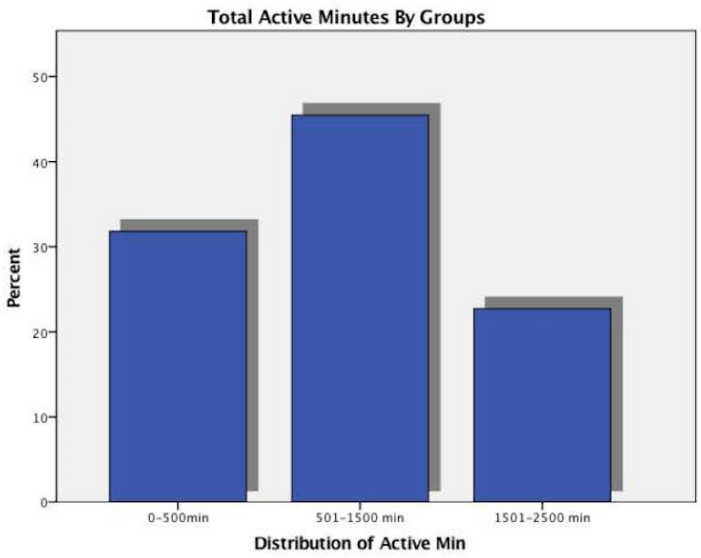
6; TNF- α = Tumor Necrosis Factor- α; FACT-Cog Version 3= Functional Assessment of Cancer Treatment- Cognition Version 3; PCI= Perceived Cognitive Impairments Subscale; PCA= Perceived Cognitive Abilities Subscale; Others= Comments from Others Subscale, Impact= Impact on Quality of Life; HVLT=Hopkins Verbal Learning Test; COWAT= Controlled Oral Word Association Test; TMT= Trail Making Test

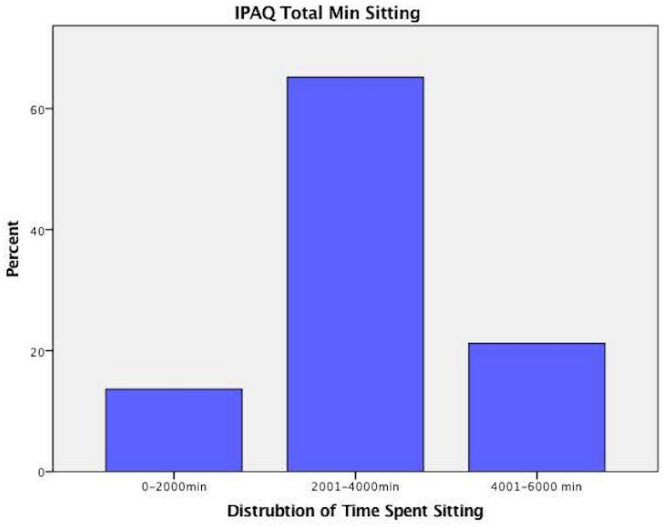
◆ For the Shapiro-Wilk Test, the null hypothesis of this test is that the population is normally distributed. Thus, if the p-value is less than the chosen alpha level then the null hypothesis is rejected and there is evidence that the data tested are not from a normally distributed population

^ Fact Cog Total: lower scores indicate lower overall functioning; PCI: lower scores indicate worse cognitive impairments; Impact on QOL: Higher scores, better QOL lower scores worse QOL; Comments from Others: lower scores, worse comments from others ; PCA: Higher scores, better abilities, lower scores worse perceived abilities

Appendix N. IPAQ Frequency Bar Graphs

Appendix N





Appendix O. Outliers Table

Appendix O

Predictor Variables and Dependent Variables Outliers and Assumptions (n=66)

	Outliers: Box plots	Shapiro-Wilk Test of Normality Met?	Transformation Y/N	Specific Transformation
BMI	-	No	N	-
HWR	20, 38, 56, 57	No	N	-
Yrs Ed	13, 18, 44, 50	No	N	-
PROMIS Anxiety	-	No	N	-
PROMIS Depressive	9, 17	No	N	-
PROMIS Fatigue	-	Yes	N	
PSQI Total	-	No	N	-
IPAQ Tot Min Act	17, 32, 35, 44	No	N	-
IPAQ Tot Min Sit	4, 23, 25, 18	Yes	N	-
UCLA-R	-	No	N	-
PSS	-	No	N	-
ESS	-	No	N	-
IL-6	56, 7, 52, 12, 23	No	Y	Log 10
IL-6 log 10	20, 37, 31, 47		Y	Log 10
TNF-α	27	Yes	Y	Log 10
TNF-α log 10	32		-	-
IL-6* TNF-α	7,12,56	No	-	-
IL-6* TNF-α (log10 scores)	20, 31,37, 47		-	-
FACT-Cog	-	Yes	N	-
HVLT-I	-	Yes	N	-
HVLT -D	40	No	N	-
COWAT	19, 60	Yes	N	-
Trails A	25, 52	No	Y	Sq rt
Trails B	25, 43	No	Y	Log 10

Appendix P. Independent T test Results for Covariate Selection

Appendix P

Group Differences in Outcome Variables (n=66)

Measure	Mean (SD)	Mean (SD)	*t*	*p value*
	Anthra (n=37)	Non-Anthra (n=29)		
FACT-Cog Total	97.80 (33.29)	91.39 (37.07)	-0.73	0.47
PCI	49.61 (20.05)	45.01 (22.07)	-0.87	0.39
PCA	23.00 (8.35)	21.97 (9.39)	-0.47	0.64
HVLT-Immediate	29.92 (2.98)	29.66 (4.30)	-0.28	0.78
HVLT Delayed	10.73 (1.40)	10.45 (1.55)	-0.76	0.45
COWAT	52.57 (10.49)	37.14 (11.74)	-1.96	0.06#
TMT A[a]	4.86 (0.73)	5.33 (0.92)	2.51	0.03*
TMT B[b]	1.70 (0.12)	1.76 (0.16)	1.55	0.13
IL-6❖	0.11 (0.46)	0.29 (0.40)	1.77	0.08
TNF- α❖	0.78 (0.11)	0.74 (0.09)	-1.44	0.15
IL-6*TNF-α❖	0.08 (0.38)	0.23 (0.30)	1.78	0.08
	Tamoxifen (n=40)	Non-Tamoxifen (n=26)		
FACT-Cog Total	90.64(34.71)	101.66 (34.71)	1.26	0.21
PCI	45.27 (20.73)	51.16 (21.13)	1.12	0.27
PCA	21.33 (8.62)	24.43 (8.82)	1.41	0.17
HVLT-Immediate	30.05 (3.71)	29.42 (3.45)	-0.70	0.49
HVLT Delayed	10.68 (1.49)	10.50 (1.45)	-0.48	0.64
COWAT	39.53(10.97)	41.19 (11.92)	0.57	0.57
TMT A[a]	5.09 (0.75)	5.02 (0.98)	-0.28	0.78
TMT B[b]	1.74 (0.14)	1.71 (0.15)	-0.80	0.43
IL-6❖	0.20 (0.34)	0.17 (0.57)	-0.22	0.83
TNF- α❖	0.75 (0.11)	0.78 (0.09)	1.17	0.25

Appendix P. Independent T test Results for Covariate Selection

IL-6*TNF-α❖	0.15 (0.27)	0.14 (0.45)	-0.07	0.95
	Abdominal Obesity (n=13)	No Abdominal Obesity (n=53)		
FACT-Cog Total	99.47 (33.56)	94.01 (35.71)	0.50	0.63
PCI	49.39 (22.34)	47.23 (21.00)	0.31	0.76
Abilties	24.83 (7.17)	22.19 (9.08)	1.09	0.29
HVLT-Immediate	31.08 (2.64)	29.58 (3.74)	1.63	0.12
HVLT Delayed	11.00(1.86)	10.51 (1.38)	0.86	0.40
COWAT	46.67 (12.54)	39.17 (10.21)	1.93	0.07#
TMT A[a]	4.83 (0.78)	5.08 (0.81)	-1.01	0.33
TMT B[b]	1.70 (0.13)	1.73(0.14)	-0.56	0.58
IL-6❖	0.10 (0.46)	0.21 (0.46)	-0.76	0.46
TNF- α❖	0.81 (0.08)	0.75 (0.11)	2.24	0.04*
IL-6*TNF-α❖	0.08 (0.36)	0.16 (0.35)	-0.69	0.50
	Pre-menopause (n=19)	Post-menopause (n=47)		
FACT-Cog Total	97.40 (39.40)	94.01 (33.28)	-0.33	0.74
PCI	49.19 (22.42)	46.94 (20.51)	-0.38	0.71
PCA	23.47 (10.12)	22.17 (8.25)	-0.50	0.62
HVLT-Immediate	28.89 (3.25)	30.17 (3.70)	1.39	0.17
HVLT Delayed	10.26 (1.37)	10.74 (1.50)	1.26	0.22
COWAT	38.21 (10.56)	40.98 (11.59)	0.94	0.36
TMT A[a]	4.89 (0.48)	5.14 (0.95)	1.37	0.18
TMT B[b]	1.71 (0.08)	1.73 (0.16)	0.68	0.50
IL-6❖	0.22 (0.38)	0.17 (0.47)	-0.42	0.68
TNF- α❖	0.79 (0.12)	0.75 (0.10)	-1.26	0.22
IL-6*TNF-α❖	0.19 (0.32)	0.13 (0.36)	-0.69	0.51

Note. IL-6= Interleukin 6; TNF-α = Tumor Necrosis Factor- α; FACT-Cog= Functional Assessment of Cancer Treatment- Cognition; PCI= Perceived Cognitive Impairments Subscale of the FACT-Cog; PCA=

Appendix P. Independent T test Results for Covariate Selection

Perceived Cognitive Abilities of the FACT-Cog; HVLT=Hopkins Verbal Learning Test; COWAT= Controlled Oral Word Association Test; TMT= Trail Making Test PSQI Total scales

❖Log_{10} transformed data

* $p<.05$; # $p<0.10$

a= Transformed data used (sq rt transformation)

b= Transformed data used (log 10 transformation)

Appendix Q. Covariates for Aim 3Covariates for Aim 3

Appendix Q

Covariate Selections for Dependent Variables in Aim 3

Outcome (Dependent Variable)	Covariate Selection
FACT-Cog Total	BMI
PCI	BMI
PCA	BMI
HVLT-Immediate	Years Education, ethnicity
HVLT Delayed	Age, Yrs Education, race
COWAT	Yrs Education, Anthracycline Chemo, Ethnicity
TMT A[a]	Age, Anthracycline Chemo
TMT B[b]	Age

Note. Individual factors were were selected as covariates separately depending on the outcome variable, or the dependent variable, used in each of the regression analyses for Aim 3. The covariates were selected based on exploratory correlation analyses and also significant t tests.
a= Transformed data used (sq rt transformation)
b= Transformed data used (log 10 transformation)

Appendix R. Correlational analyses between all the PSQI subscales and the cognitive outcomes

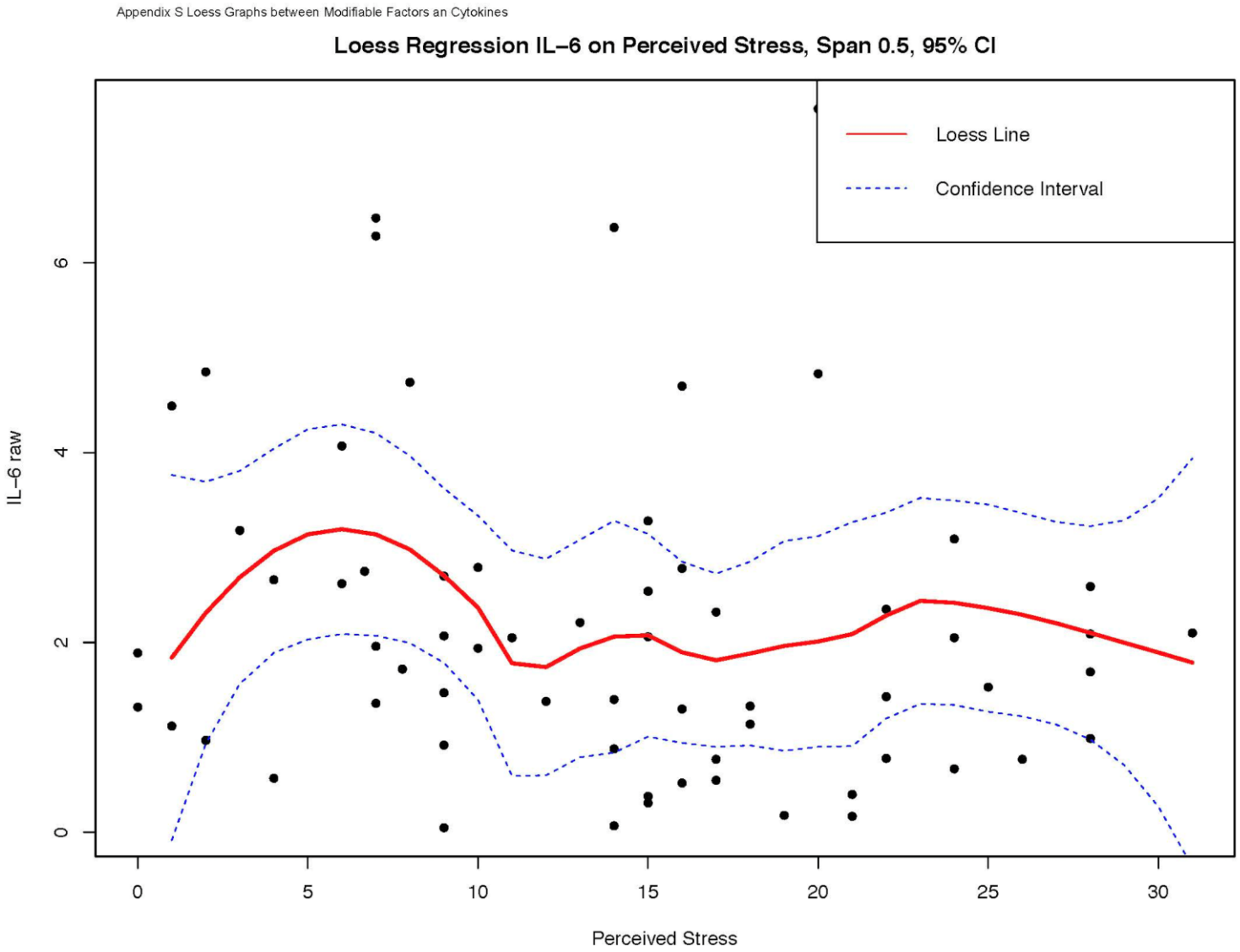
Appendix R

Pearson's Correlations between PSQI Subscales and Cognitive Outcomes (N=75)

	FACT-Cog	HVLT-I	HVLT-D	COWAT	TMT A[a]	TMT B[b]
PSQI Total	-0.49***	0.01	-0.22#	-0.05	0.09	0.10
Duration	-0.14	-0.12	-0.21#	-0.14	0.14	0.17
Latency	-0.38***	-0.00	-0.11	-0.06	0.02	-0.07
Efficiency	-0.39***	0.09	-0.16	-0.01	0.08	0.06
Disturbance	-0.43***	0.03	-0.12	0.05	-0.01	-0.06
Sleepaid	-0.20#	0.01	-0.17	0.05	0.16	0.24*
Daytime Dysfunction	-0.49***	-0.05	-0.04	-0.11	0.06	0.08
Sleep Quality	-0.26***	-0.03	-0.15	-0.03	-0.17	-0.09

Note. Significance not corrected for multiple comparisons for exploratory descriptive purposes.
a= Transformed data used (sq rt transformation)
b= Transformed data used (log 10 transformation)
*** $p<.001$, ** $p<.01$, * $p<.05$, # $p<0.10$

Appendix S. Loess Regression Lines Between Modifiable Factors and Cytokines



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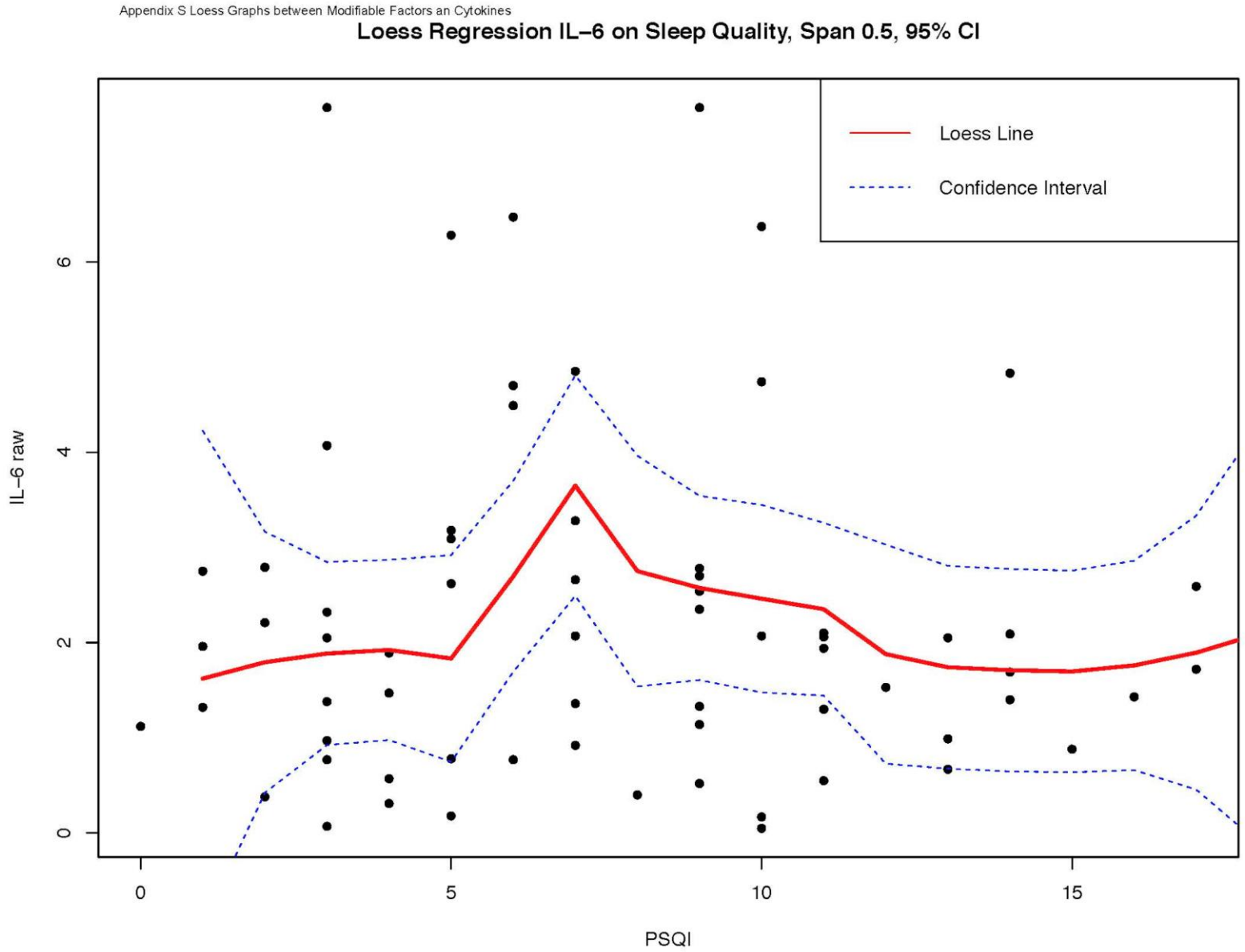

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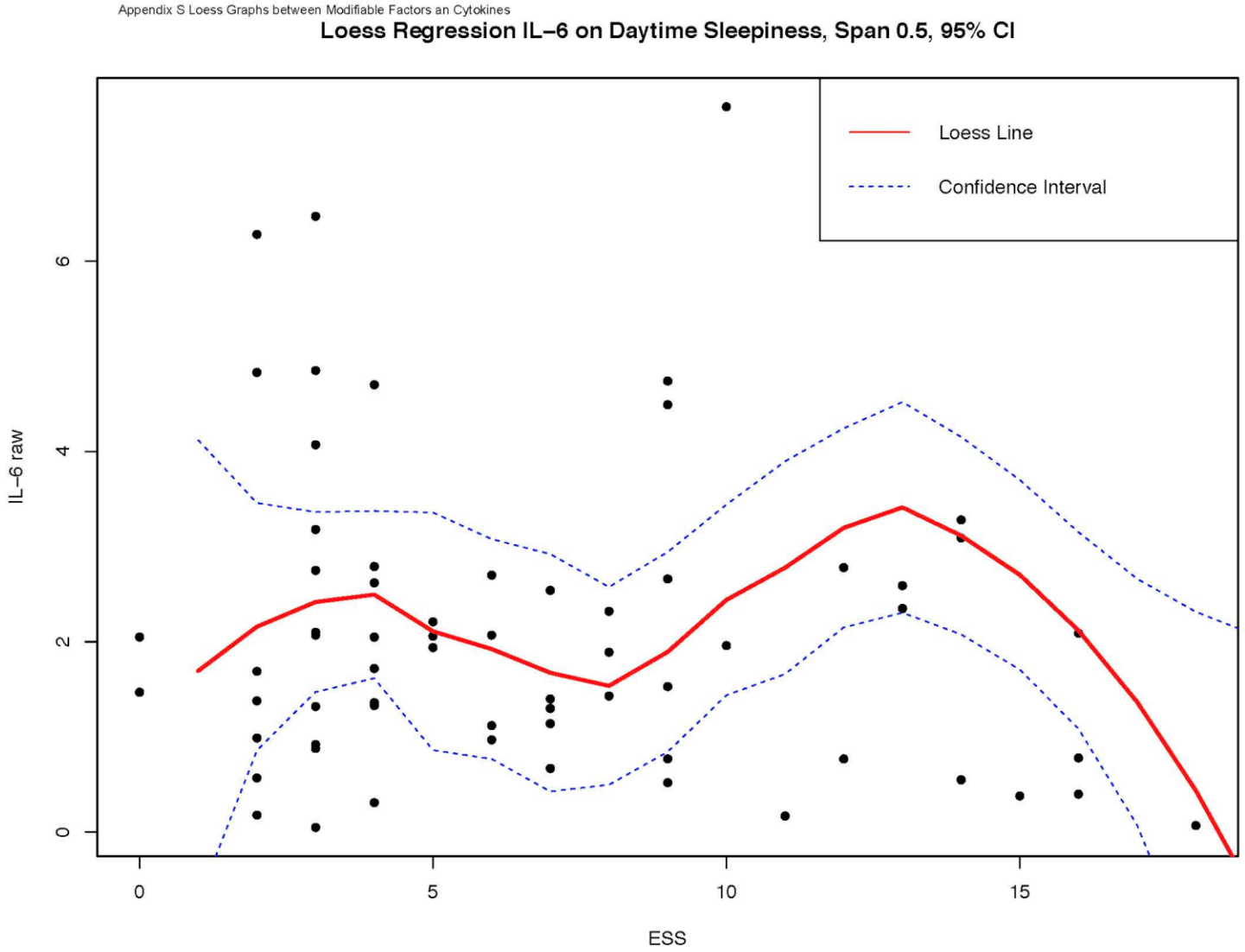

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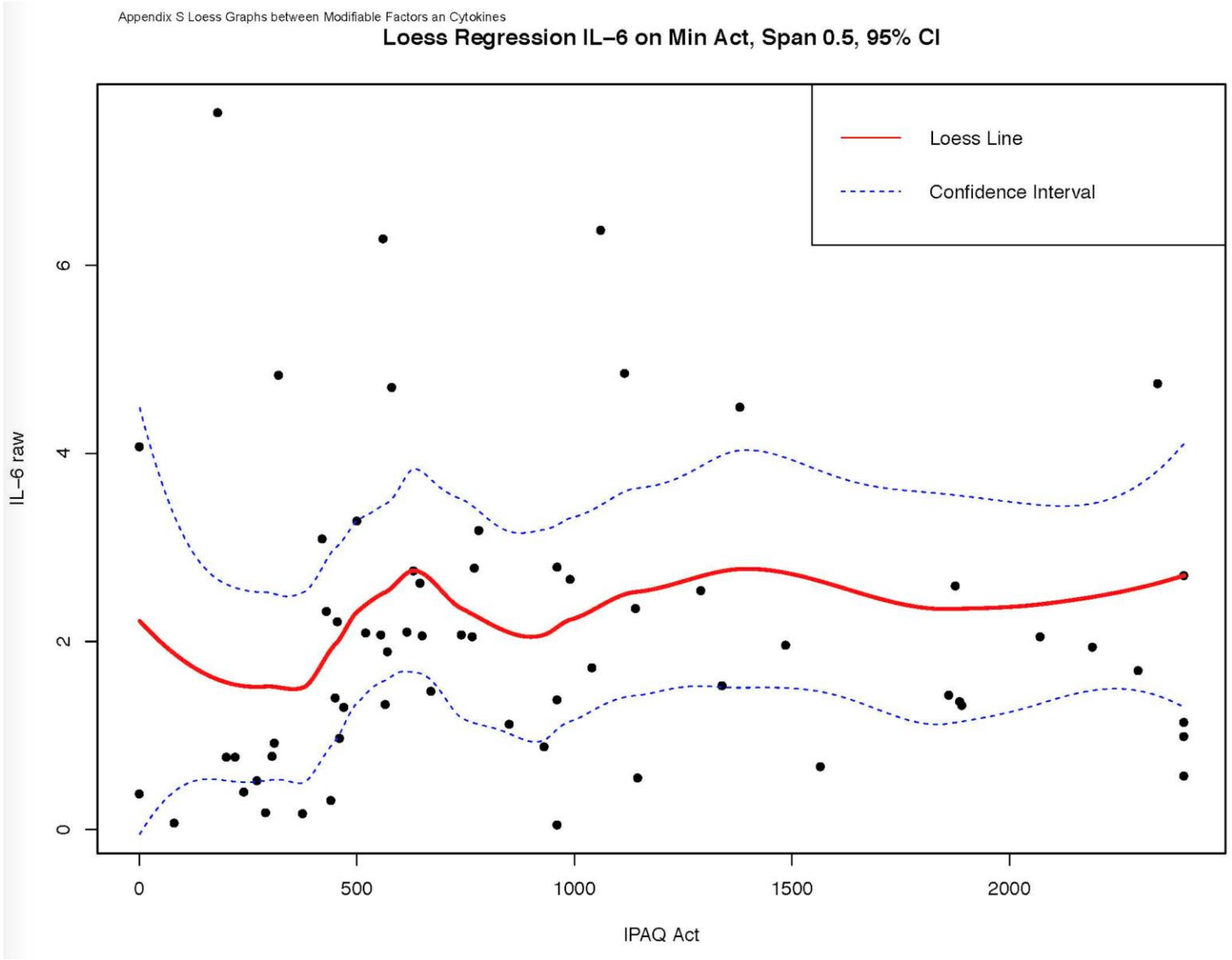

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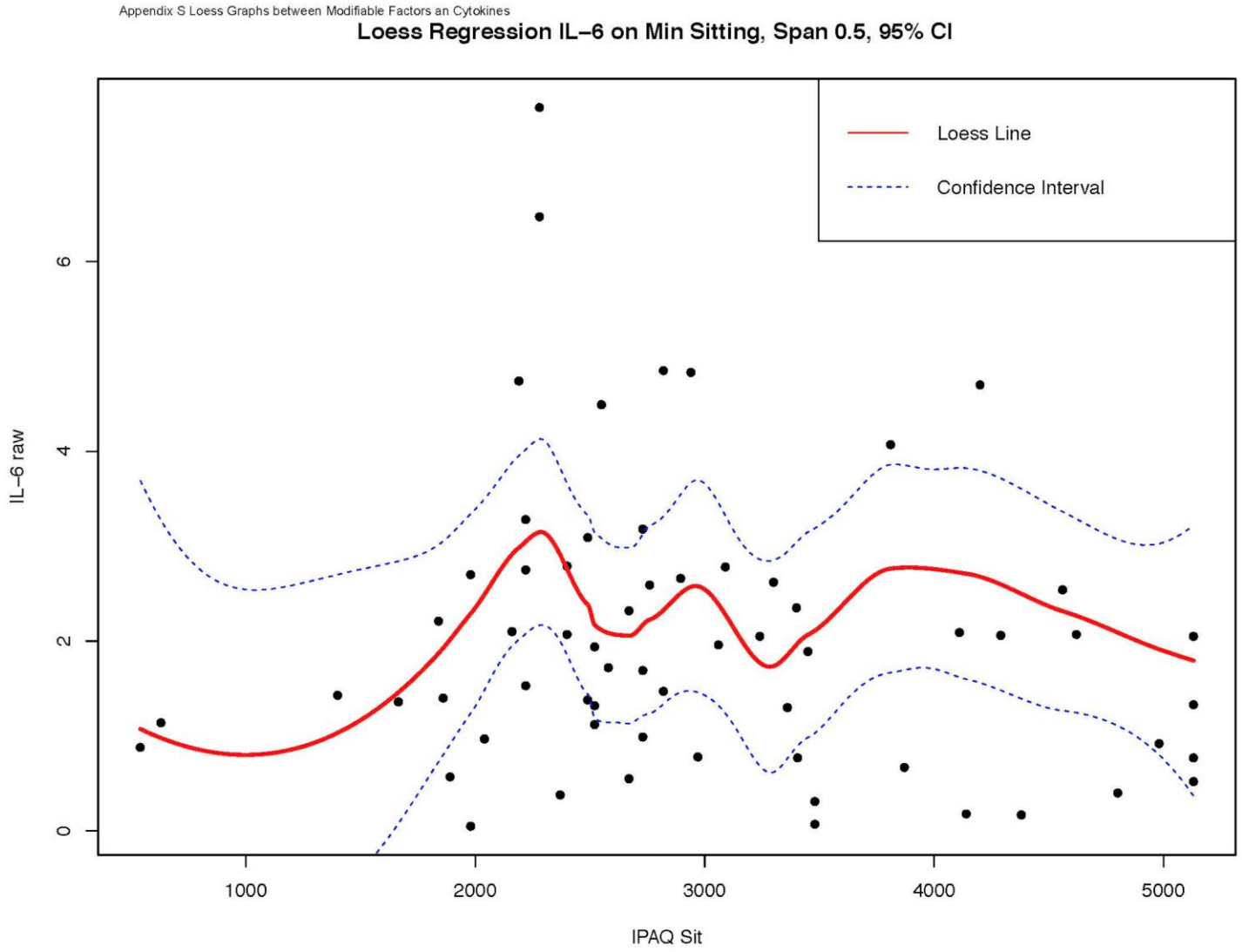

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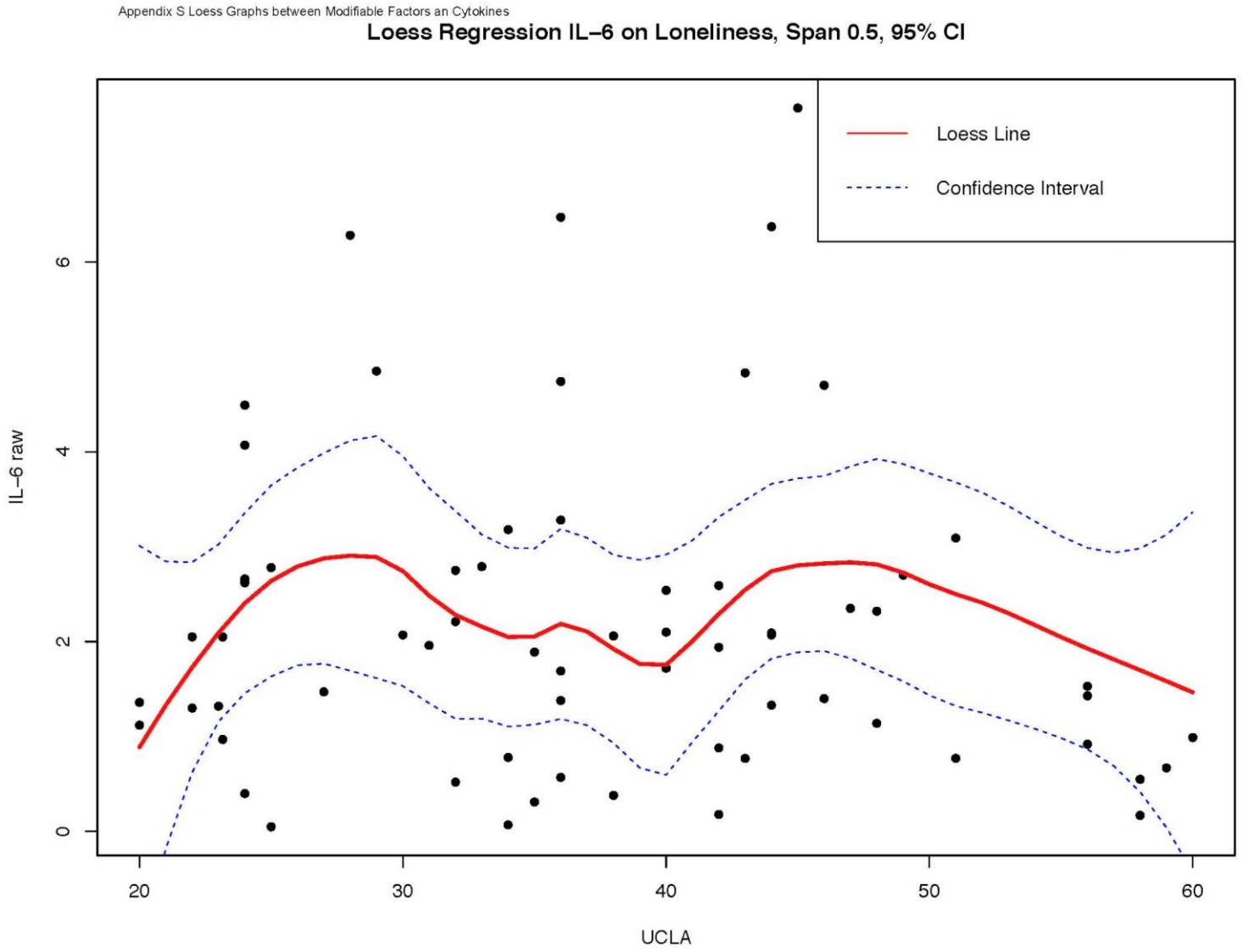
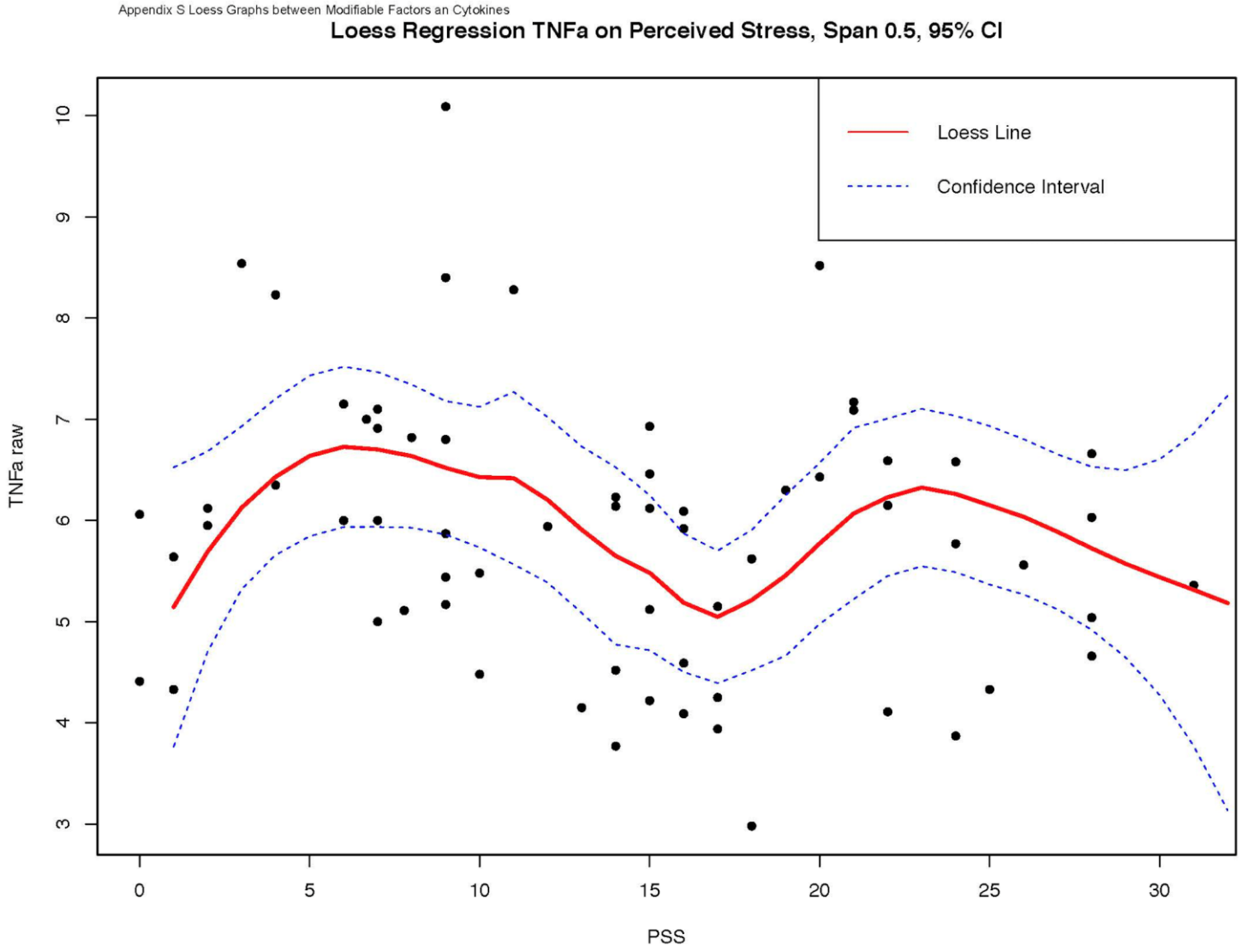
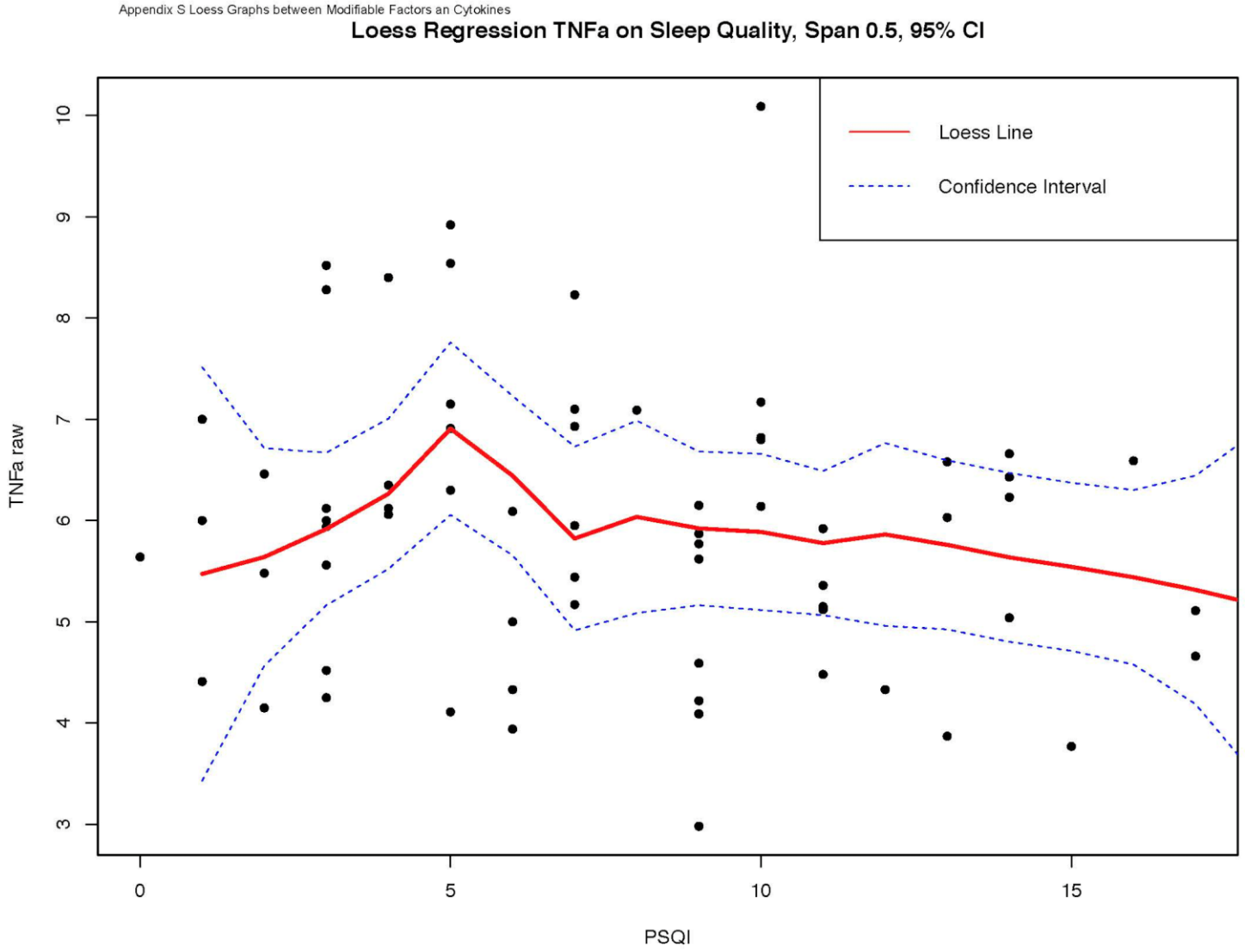


Appendix S. Loess Regression Lines Between Modifiable Factors and Cytokines



Appendix S. Loess Regression Lines Between Modifiable Factors and Cytokines



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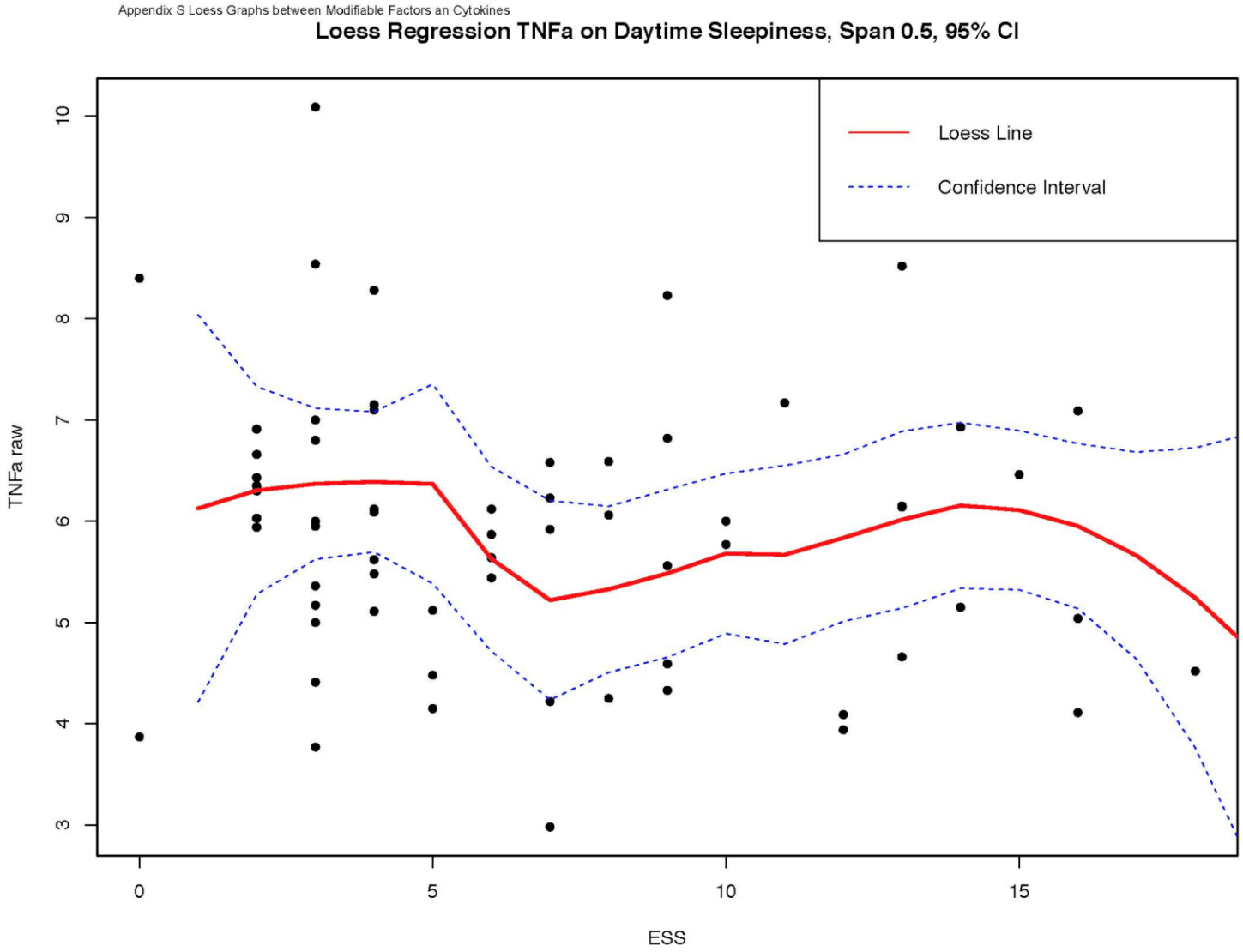

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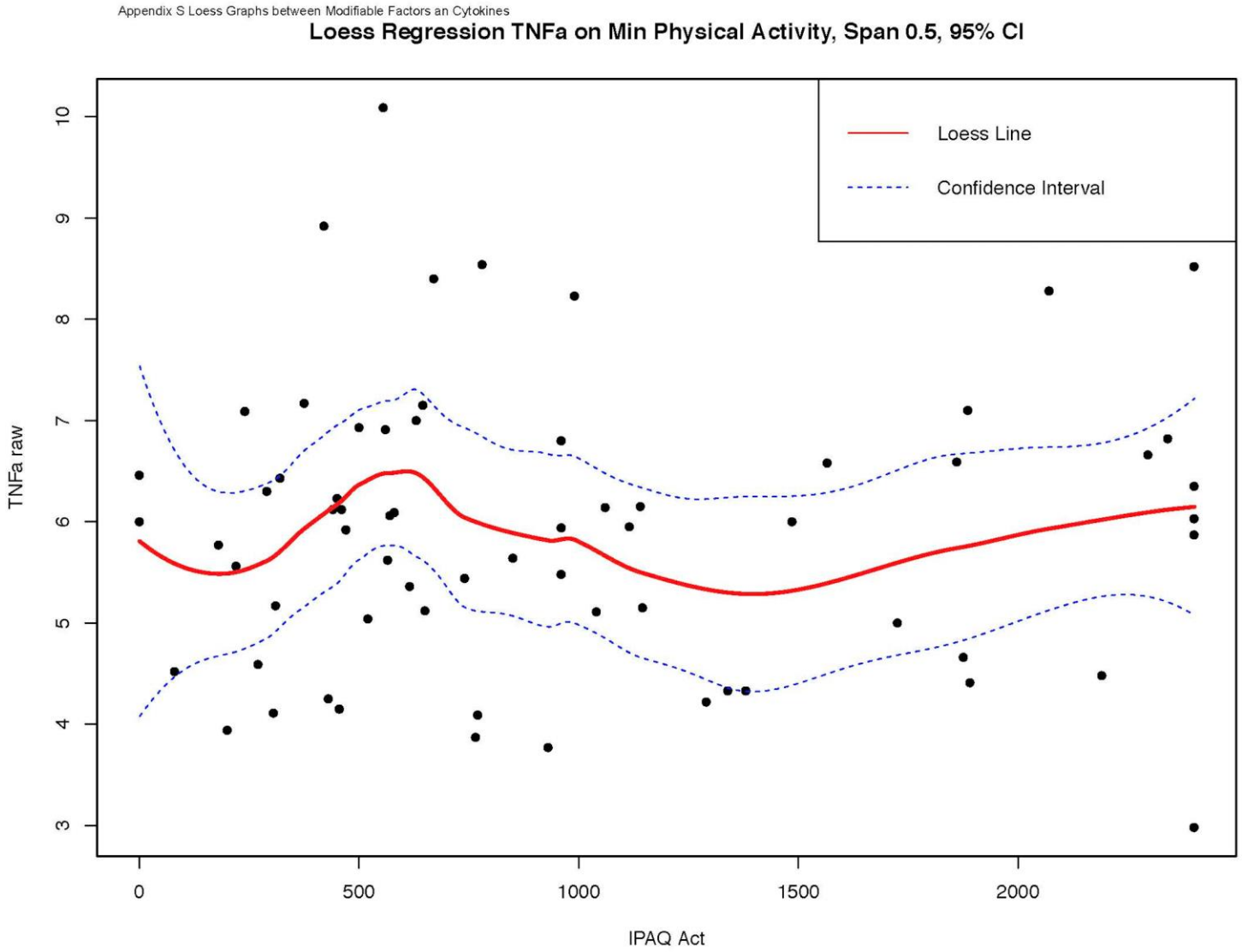

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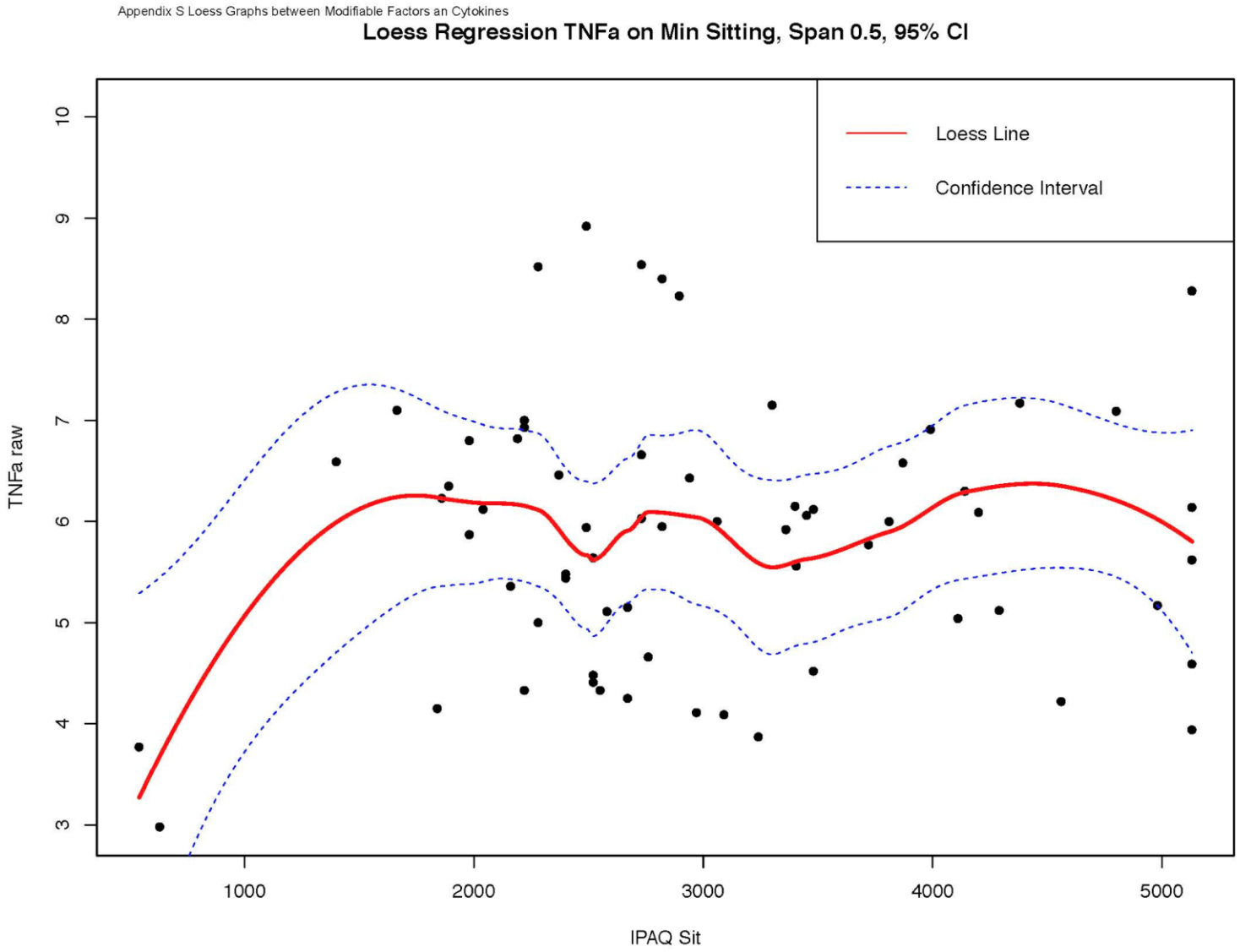

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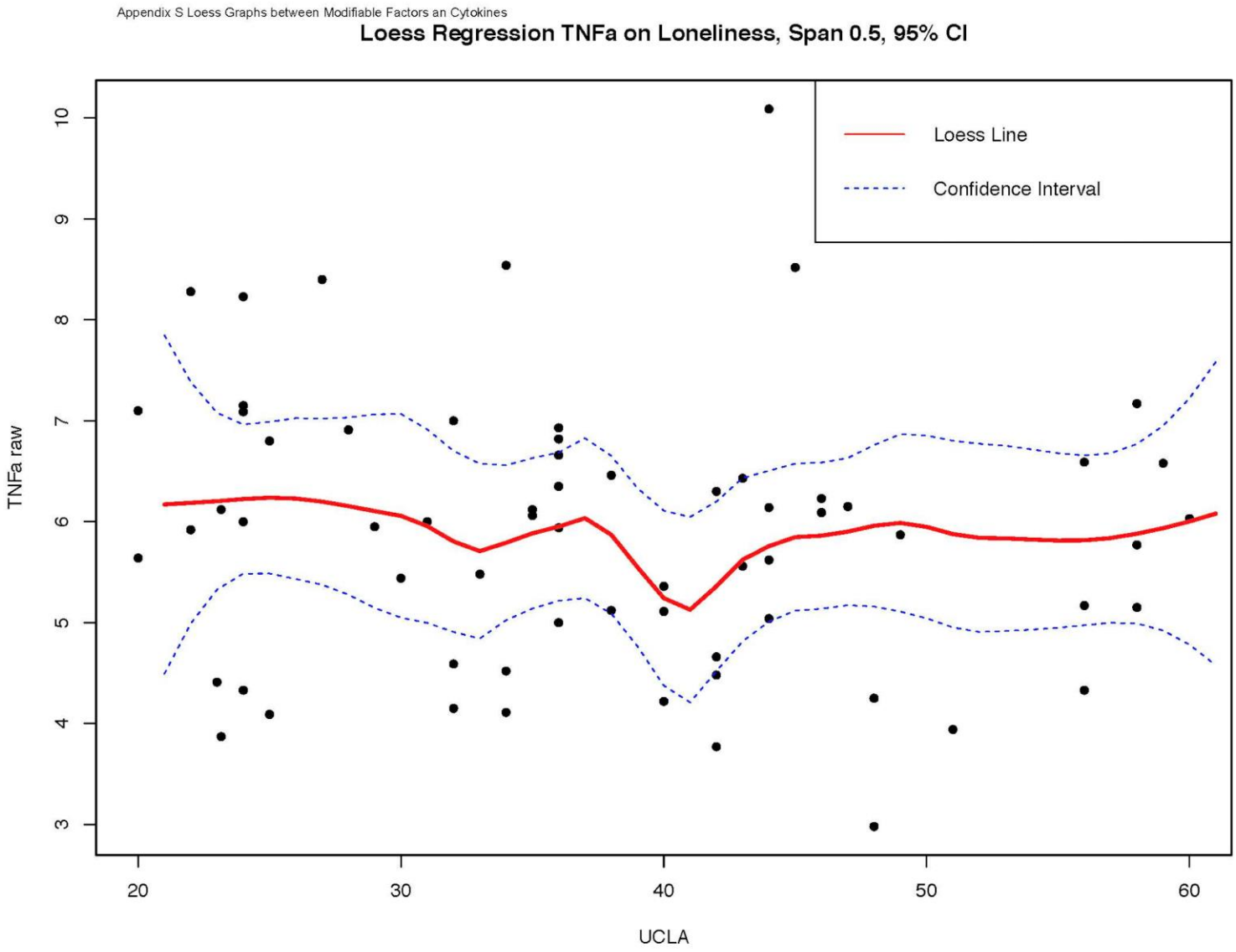
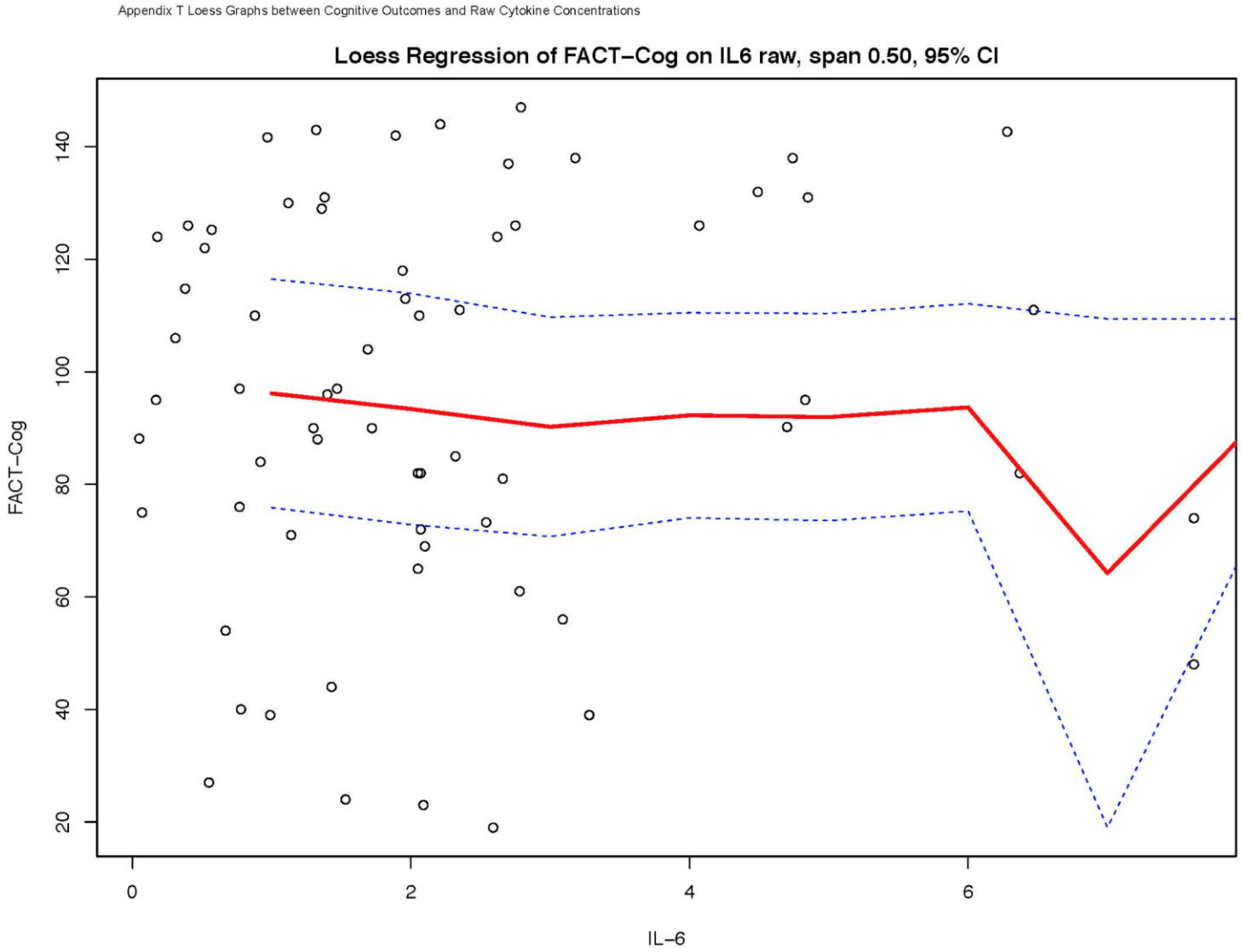
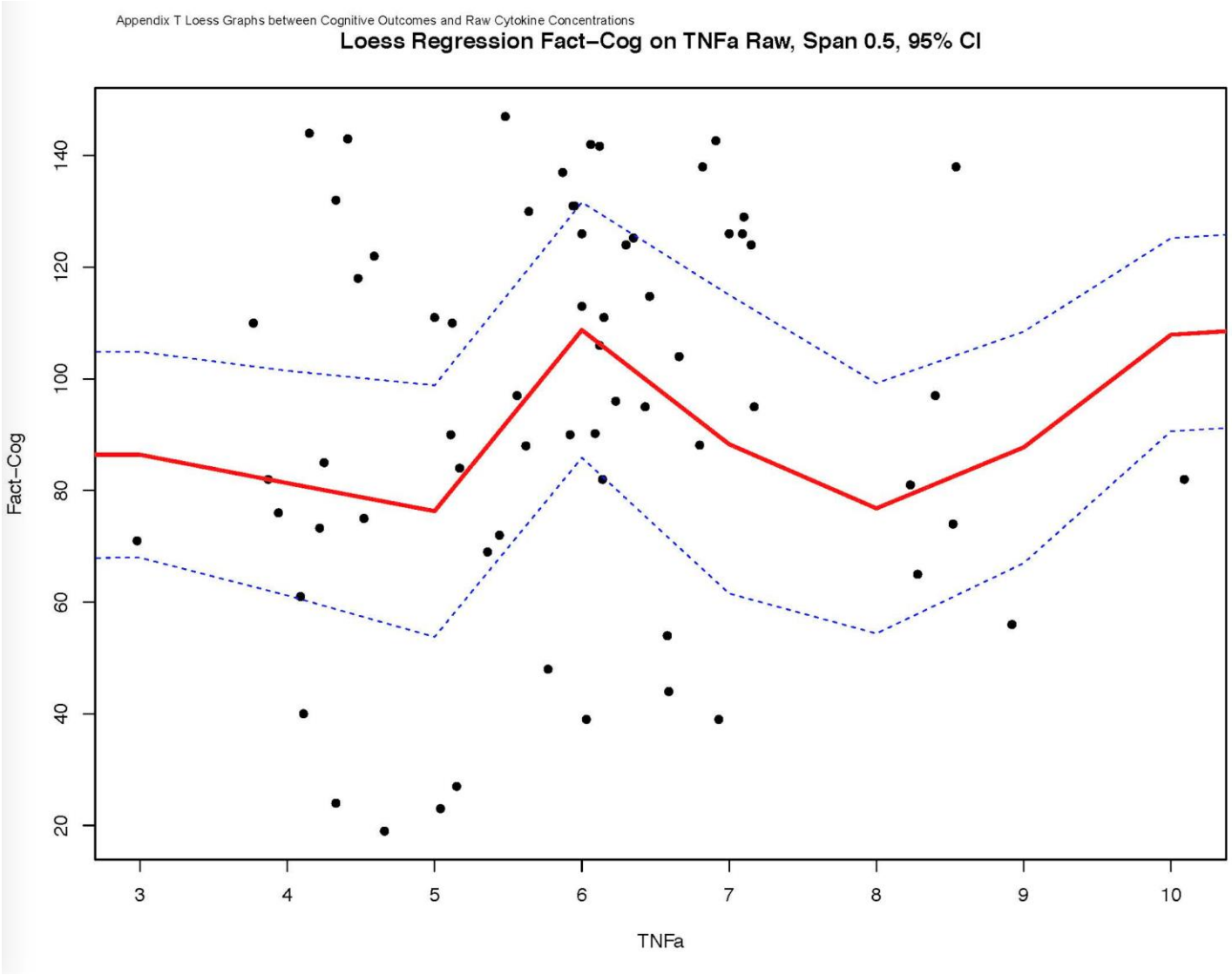


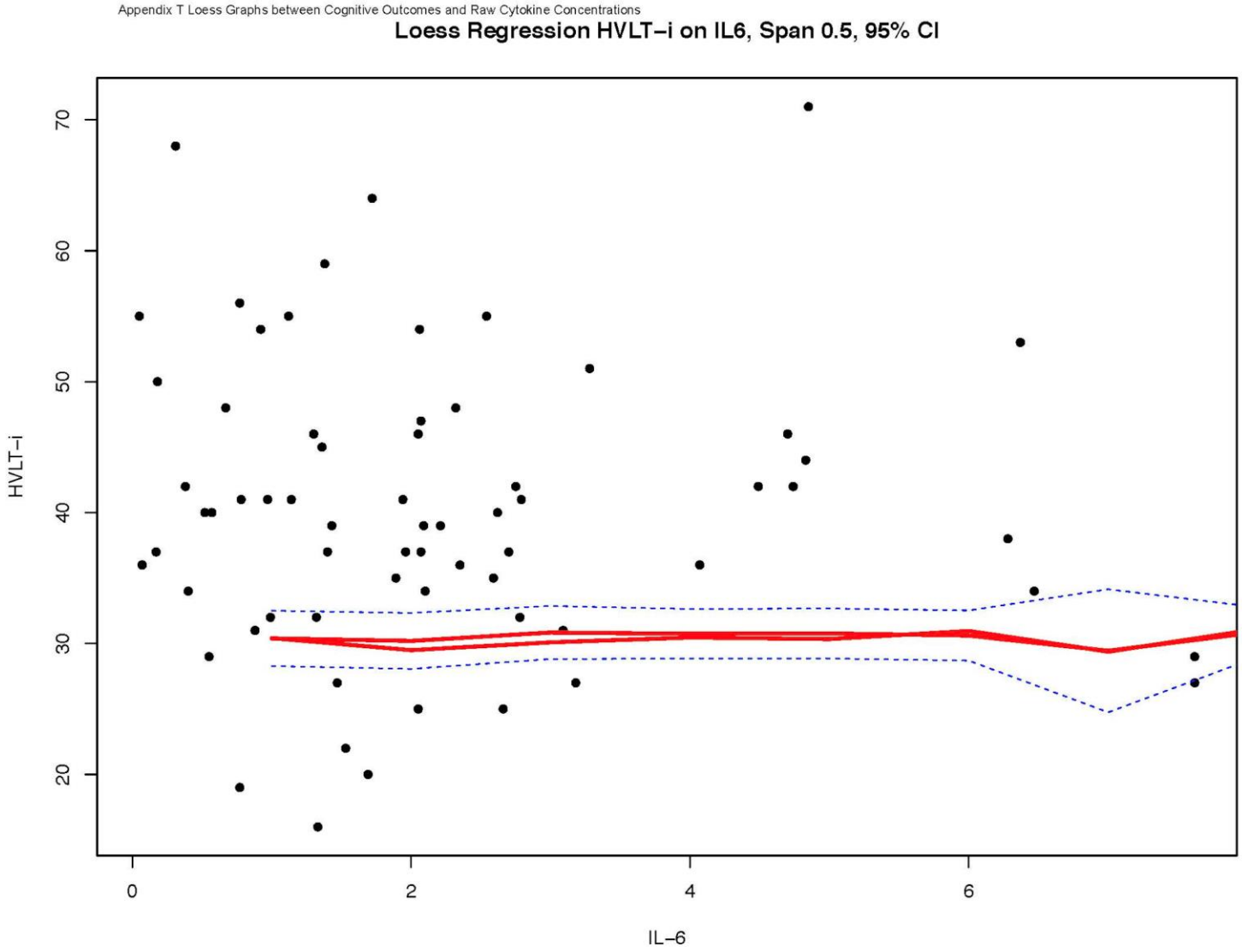
Appendix T. Loess Regression Lines Between Cytokines and Cognitive Outcomes



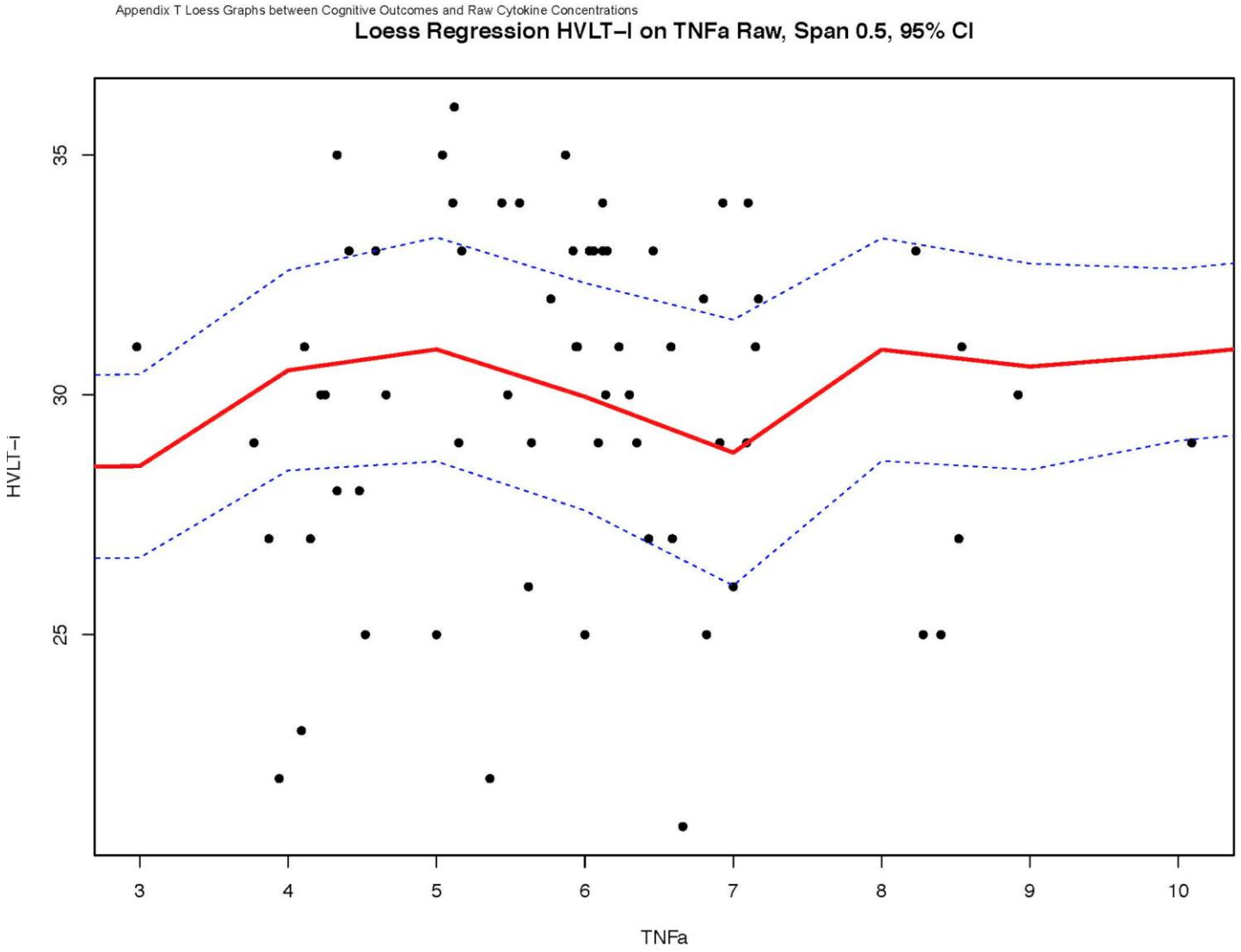
Appendix T. Loess Regression Lines Between Cytokines and Cognitive Outcomes



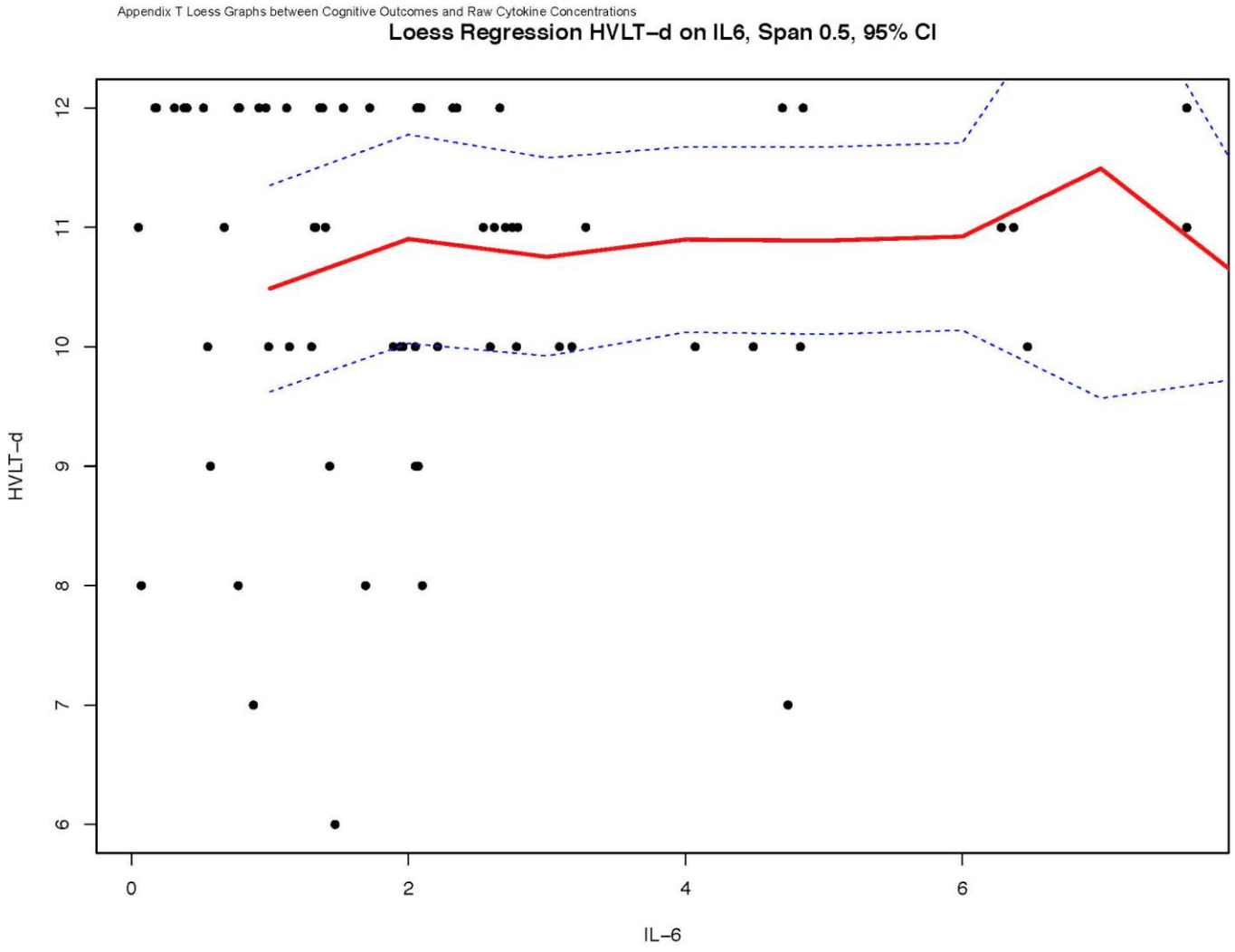
Appendix T. Loess Regression Lines Between Cytokines and Cognitive Outcomes



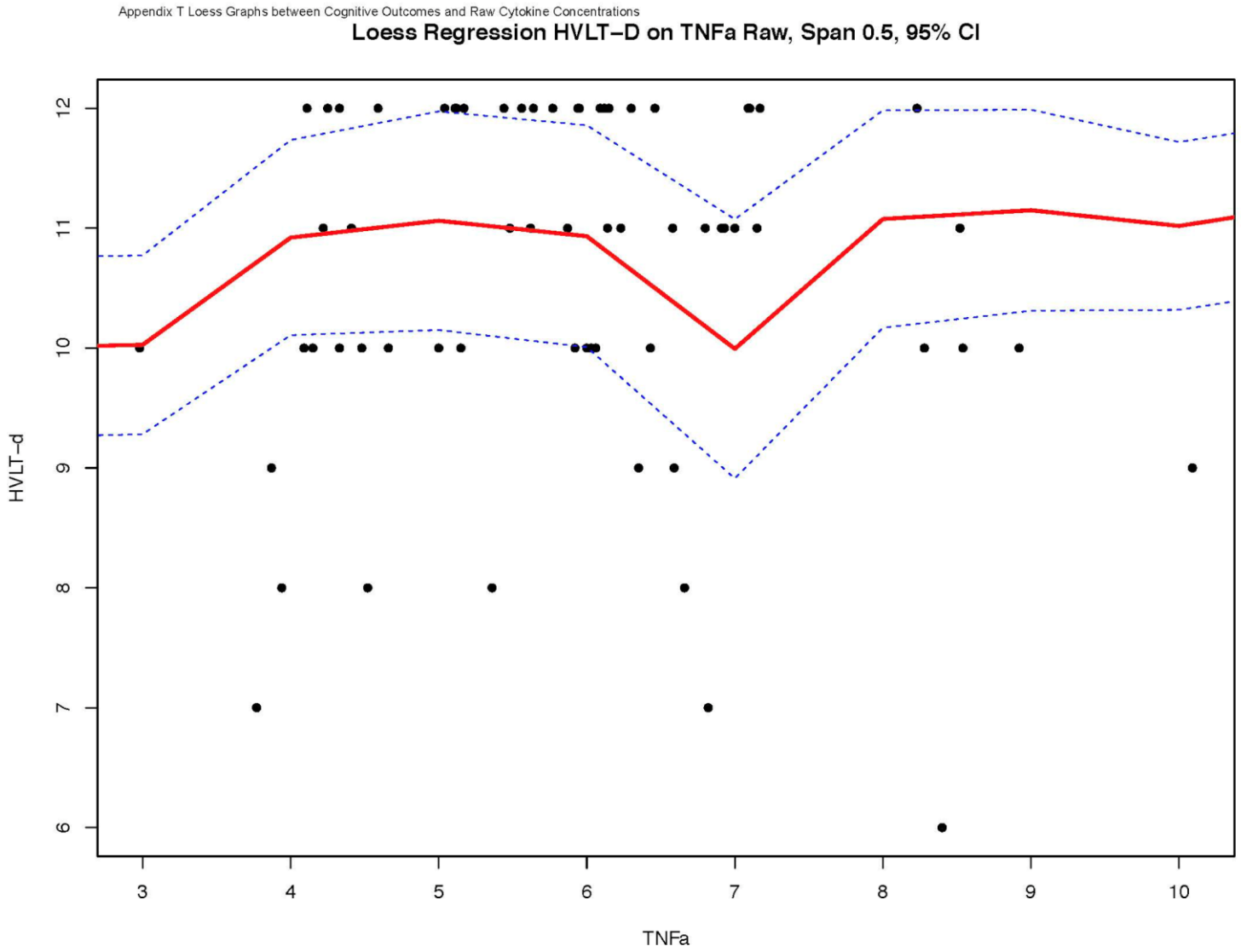
Appendix T. Loess Regression Lines Between Cytokines and Cognitive Outcomes



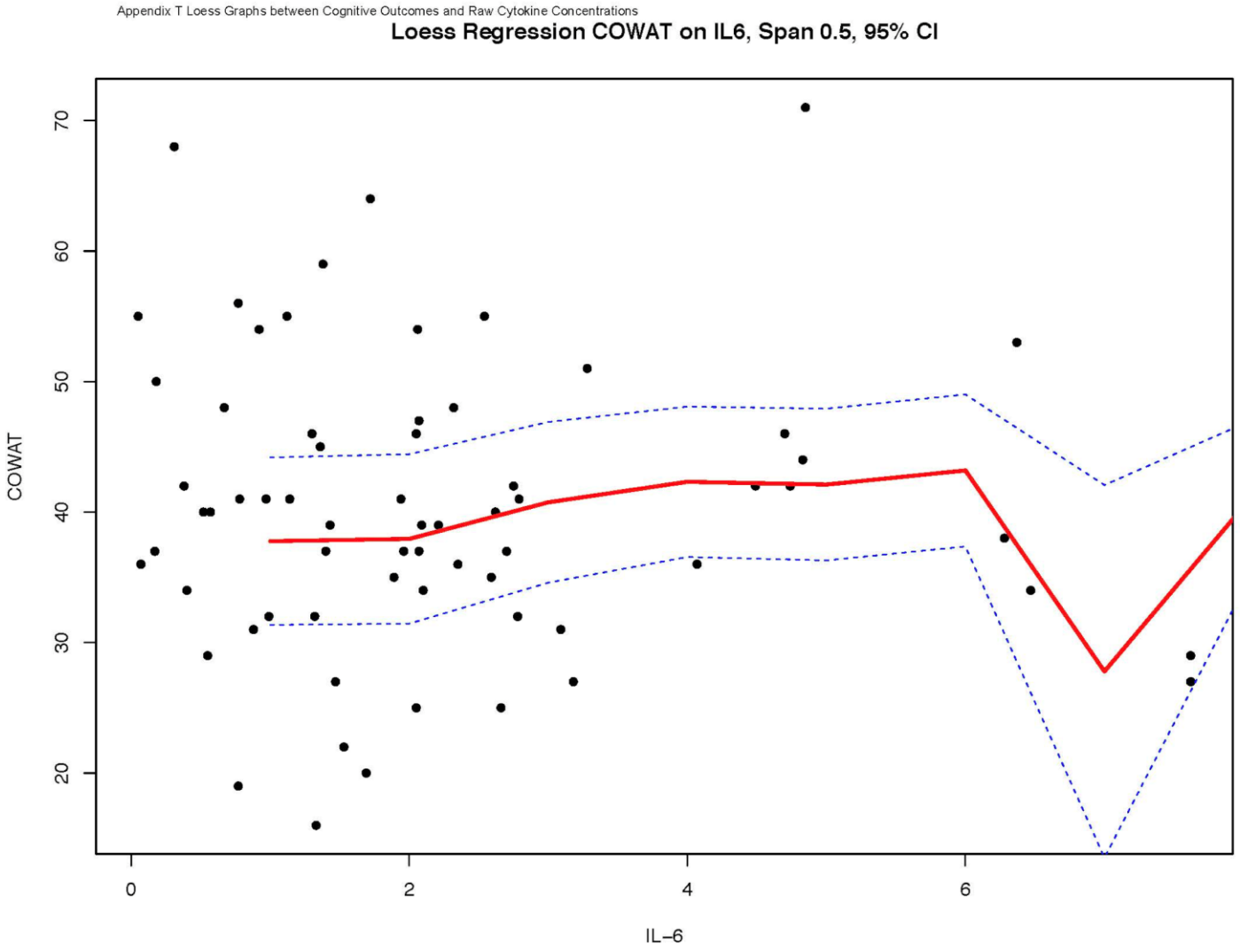
Appendix T. Loess Regression Lines Between Cytokines and Cognitive Outcomes



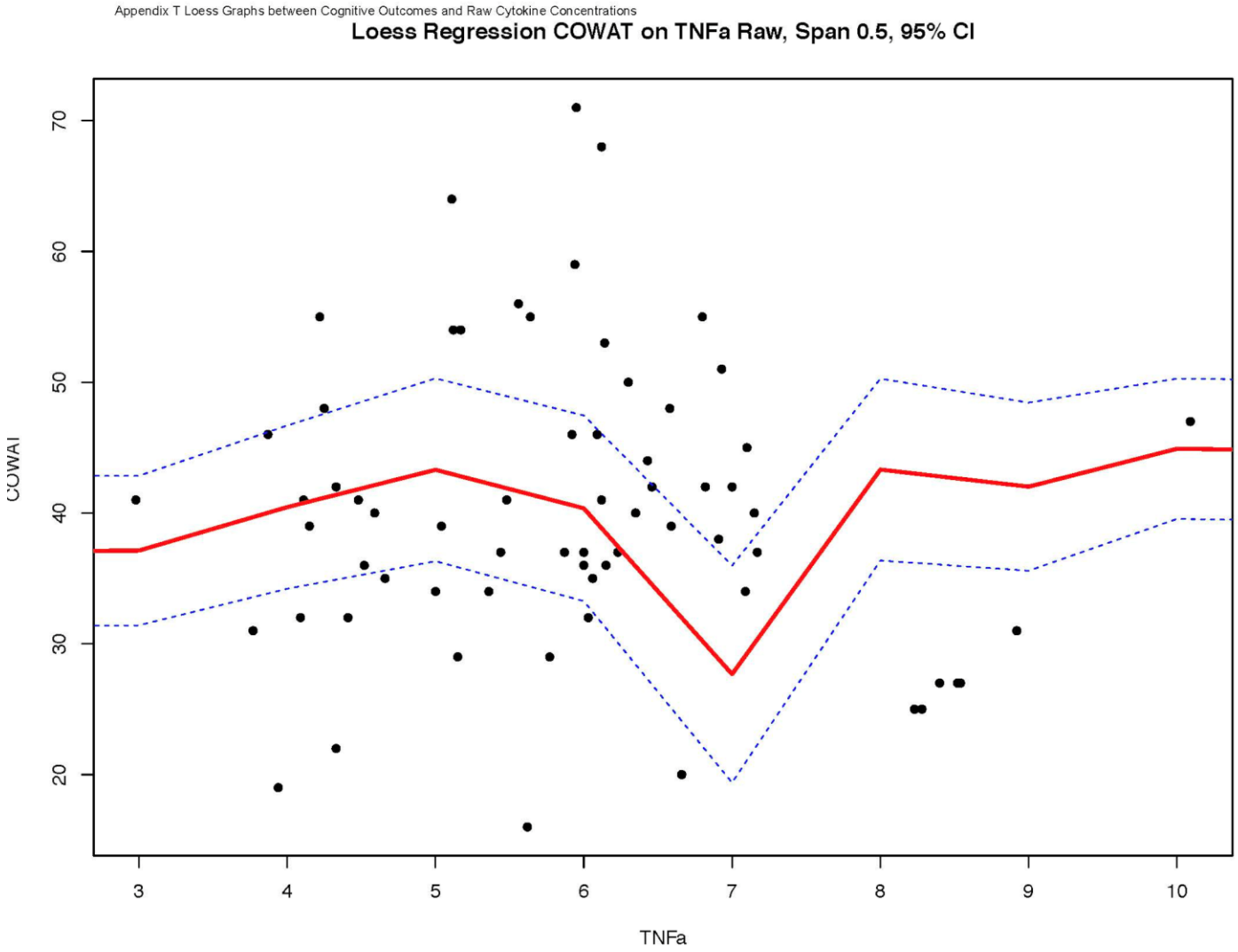
Appendix T. Loess Regression Lines Between Cytokines and Cognitive Outcomes



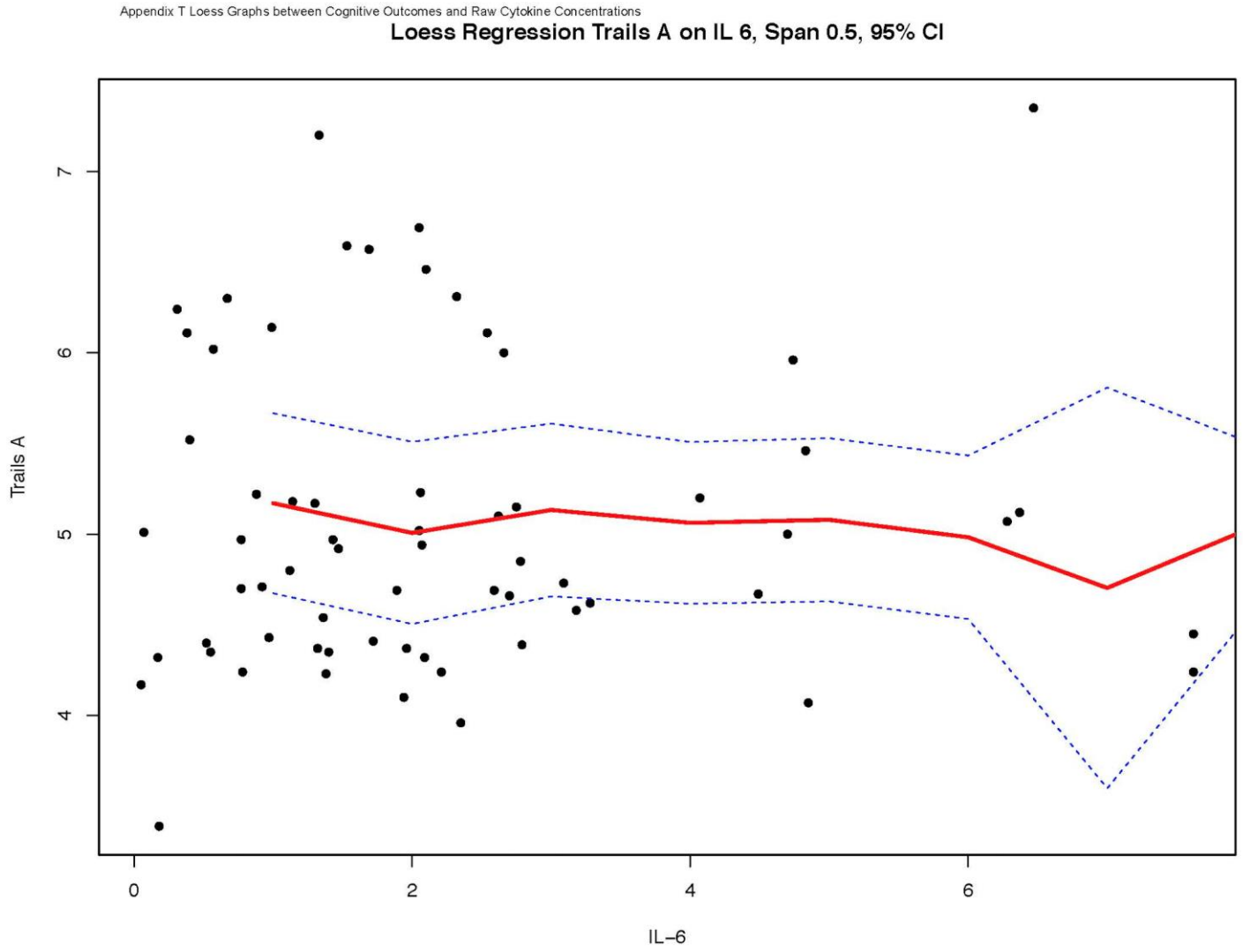
Appendix T. Loess Regression Lines Between Cytokines and Cognitive Outcomes



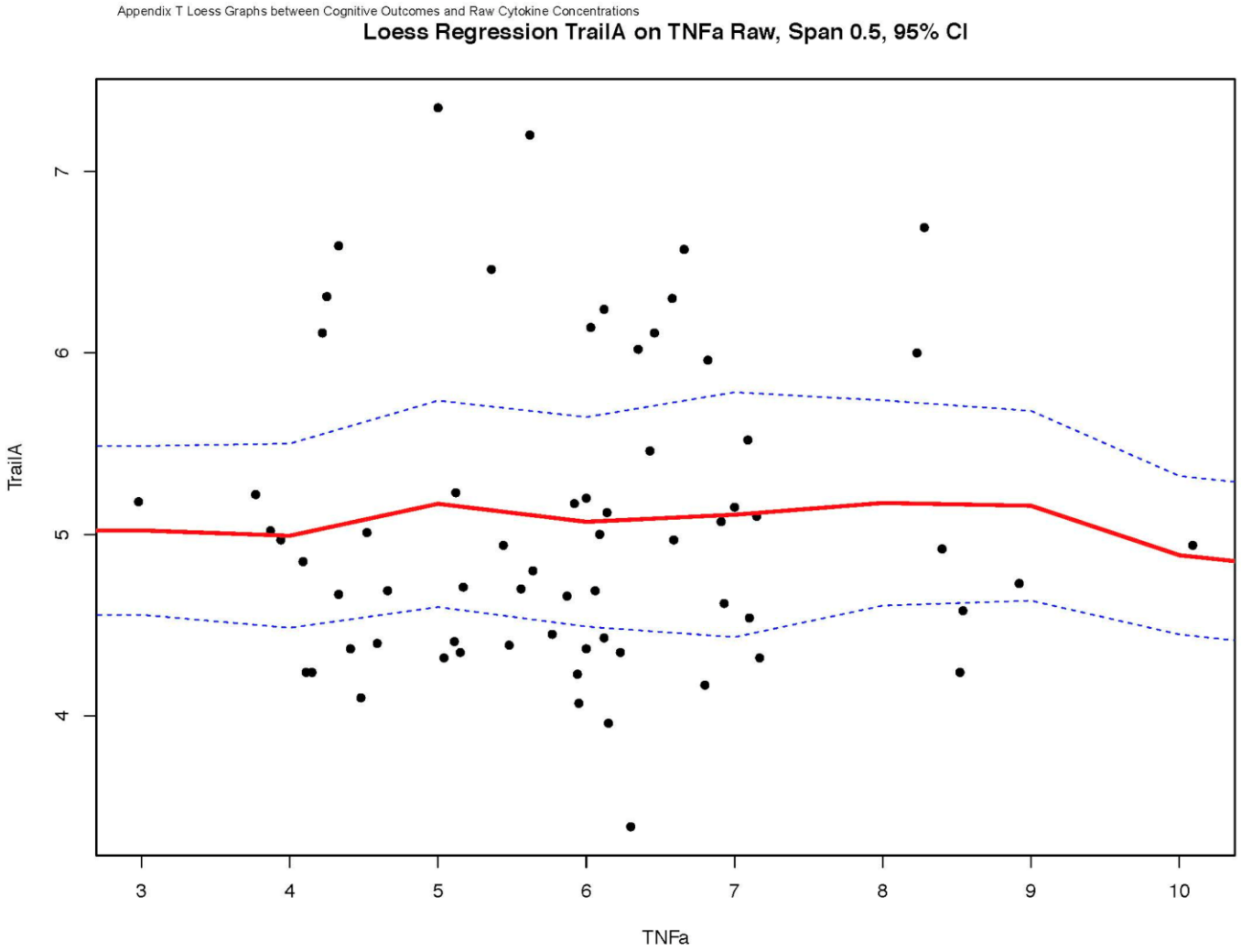
Appendix T. Loess Regression Lines Between Cytokines and Cognitive Outcomes



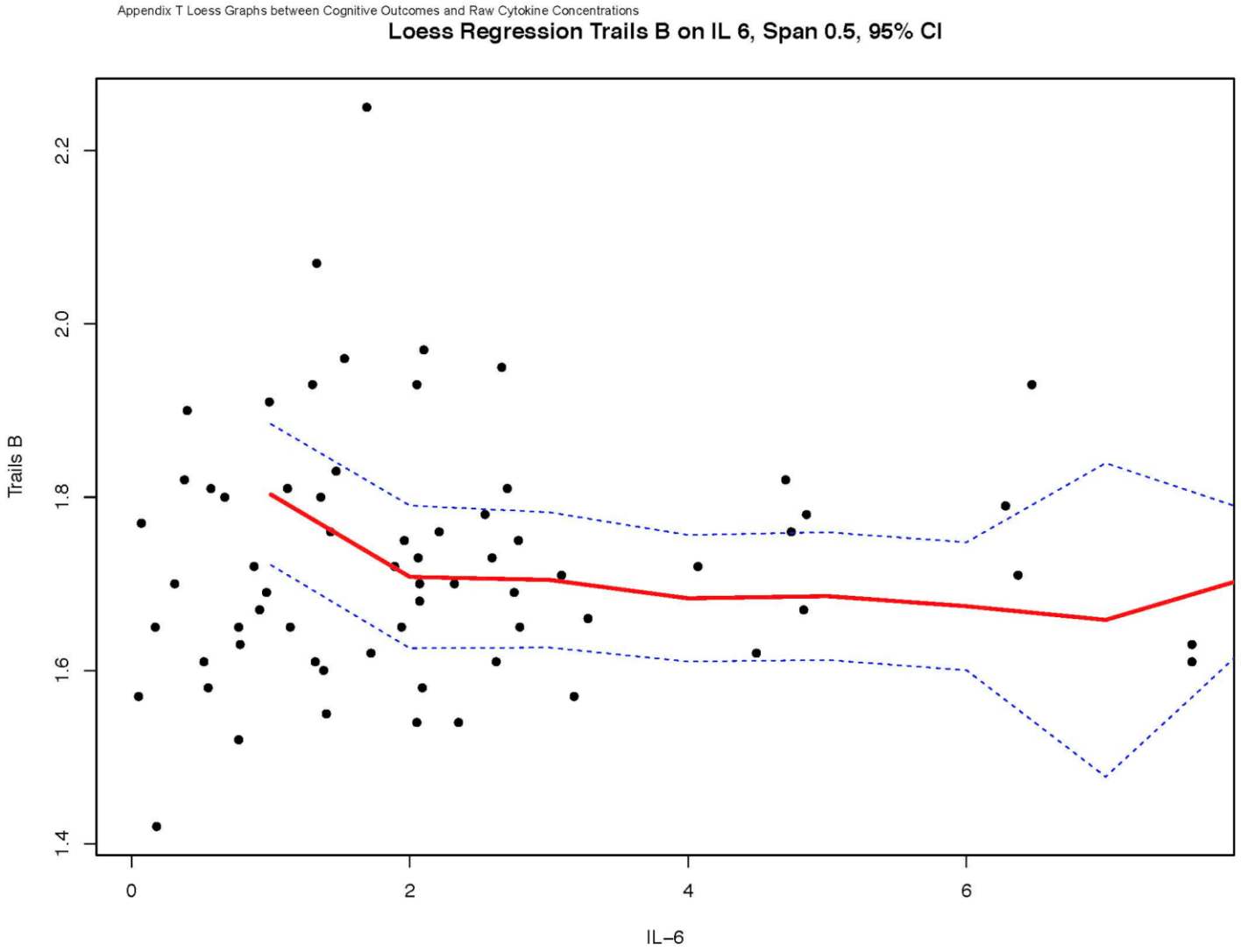
Appendix T. Loess Regression Lines Between Cytokines and Cognitive Outcomes



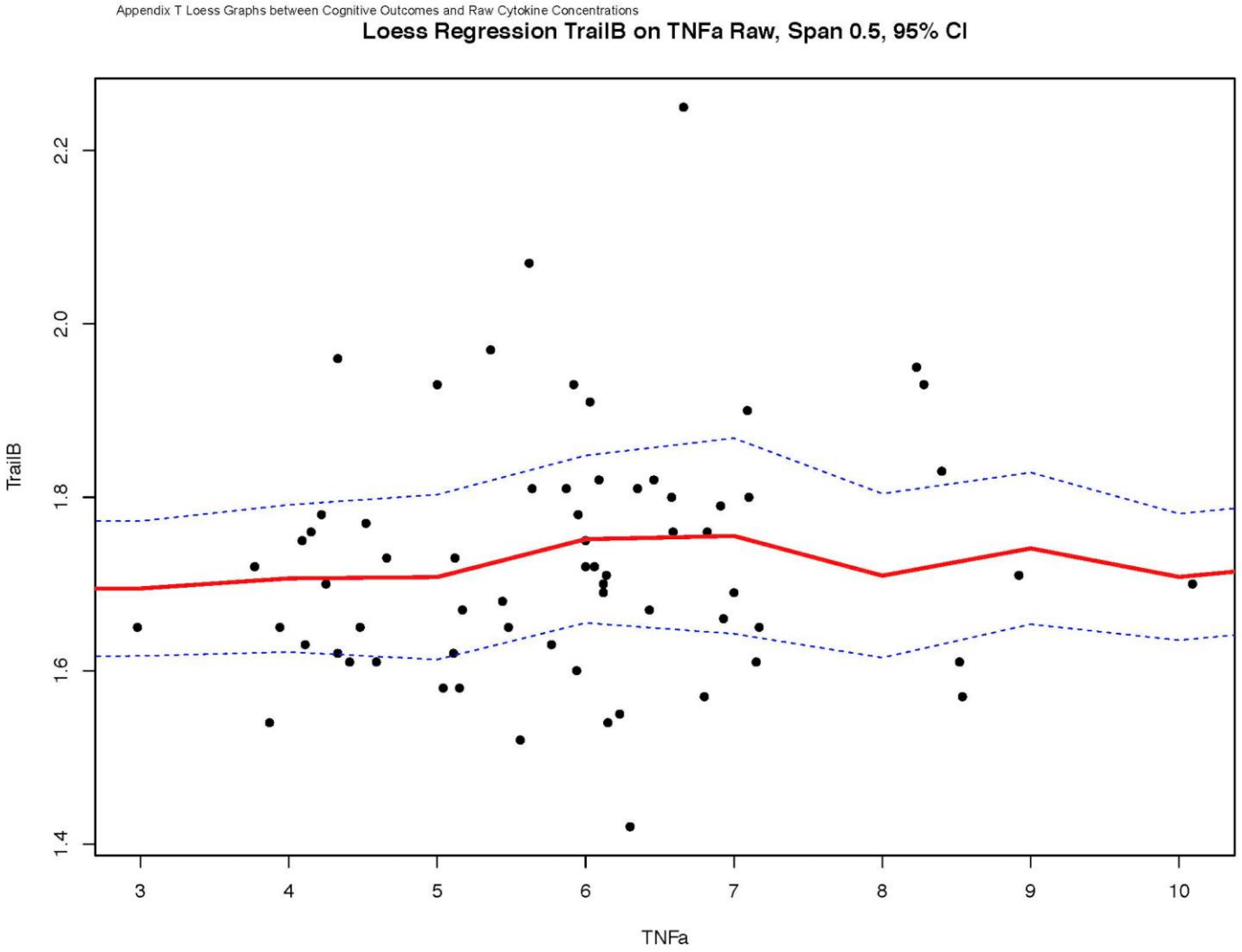
Appendix T. Loess Regression Lines Between Cytokines and Cognitive Outcomes



Appendix T. Loess Regression Lines Between Cytokines and Cognitive Outcomes



Appendix T. Loess Regression Lines Between Cytokines and Cognitive Outcomes



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